Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension

Appendices A – G

Produced by the National Collaborating Centre for Acute Care

Contents

Appendix A

SCOPE

1 Guideline title

Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension

1.1 Short title

Glaucoma

2 Background

a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Acute Care to develop a clinical guideline on the diagnosis and management of chronic open angle glaucoma and ocular hypertension for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see section 6). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued will have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) Approximately 10% of UK blindness registrations are ascribed to glaucoma. It is estimated that in the UK about 2% of people older than 40 have chronic open angle glaucoma, and this rises to almost 10% in people older than 75. With changes in population demographics the number of people affected by glaucoma is expected to rise.

b) Chronic open-angle glaucoma tends to be asymptomatic and therefore many people will not notice any symptoms until severe visual damage has occurred. Population-based screening programmes are being considered and the Department of Health's National Screening Committee is undertaking a review of screening programmes due to be published in 2007.

c) Recent national guidelines on glaucoma include 'Guidelines for the management of open angle glaucoma and ocular hypertension' (Royal College of Ophthalmologists, 2004). The Department of Health Do Once And Share project has also developed a glaucoma pathway and dataset (2006).

d) There is a clinical need for a guideline on diagnosis and management of chronic open angle glaucoma because this is a common and potentially blinding condition associated with uncertainty and variation in clinical practice in a number of areas. These include:

- an agreed case definition for ocular hypertension and chronic open angle glaucoma
- an agreed terminology incorporating the influence of raised intraocular pressure (that is, primary open angle glaucoma compared with normal tension glaucoma)
- agreement on when to treat chronic open angle glaucoma and how aggressively to do so
- agreement on whether to treat (simple) ocular hypertension
- which tests should be standard or optional for purposes of diagnosis and chronic disease monitoring
- how frequently patients should be followed up for chronic disease monitoring purposes and whether this interval should vary with perceived disease 'severity'
- who should monitor glaucoma, where this should be undertaken and whether different care providers should be used depending on perceived disease 'severity'

4 The guideline

a) The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix).

c) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Adults (18 and older) with a diagnosis of chronic open angle glaucoma or ocular hypertension. That is, individuals who, in the presence of open or narrow (but not occludable or closed) anterior chamber angles have one or more of the following features:

- glaucomatous visual field loss
- glaucomatous optic neuropathy
- raised intraocular pressure.

b) People with chronic open angle glaucoma or ocular hypertension associated with pseudoexfoliation or pigment dispersion.

c) People who have higher prevalence of glaucoma and may have worse clinical outcomes including:

- people with a family history of glaucoma,
- younger people (<50 years)
- people who are of black African or black Caribbean descent

4.1.2 Groups that will not be covered

a) People younger than 18 years.

b) People with secondary glaucoma (for example neovascular or uveitic) except for those described in 4.1.1 b.

c) People with, or at risk of, primary or secondary angle closure glaucoma.

d) Adults with primary congenital, infantile or childhood glaucoma.

4.2 Healthcare setting

a) Community, primary care, secondary care outpatient and day treatment services, and tertiary care specialist services

4.3 Clinical management

a) The diagnosis of chronic open angle glaucoma and ocular hypertension in patients presenting at community optometrists and those referred to hospital eye services using one or more of the tests below:

- measurement of intraocular pressure
- visual field test
- optic nerve head assessment
- anterior chamber angle assessment.

b) The appropriate use of pharmacological interventions, for example effectiveness, cost effectiveness, initiation and duration of treatment. Pharmacological treatments considered will include:

- eye drops
  - beta blockers
  - prostaglandin related drugs
  - sympathomimetics
  - carbonic anhydrase inhibitors
  - miotics
- systemic medications
  - carbonic anhydrase inhibitors

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only where clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform their decisions for individual patients.

c) The effectiveness of penetrating and nonpenetrating surgical drainage procedures with and without pharmacological augmentation or drainage devices.

d) The effectiveness of postsurgical drain manipulation with and without the use of pharmacological augmentation.

e) The effectiveness of laser procedures to facilitate aqueous outflow or reduce aqueous production.

f) The information, education and support needs of patients to achieve treatment concordance will be considered.

g) The most appropriate service models, where evidence of clinical and cost effectiveness is available.

h) The guideline development group will consider making recommendations on the principal complementary and alternative interventions or approaches to care relevant to the guideline topic.

i) The guideline development group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

j) Population based screening programmes for glaucoma are not within the remit of this guideline.

4.4 Status

4.4.1 Scope

This is the final scope.

4.4.2 Guideline

The development of the guideline recommendations will begin in June 2007.

Associated NICE Guidance Medicines Concordance (in development) for publication December 2008.

5 Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

6 Referral from the Department of Health

The Department of Health asked the Institute:

'To prepare a clinical guideline on the diagnosis and management of chronic open angle glaucoma and ocular hypertension (raised intraocular pressure). The guideline should include recommendations on the most appropriate service models where evidence of effectiveness is available.'

Appendix B

1 Declarations of interests

1.1 Introduction

All members of the GDG and all members of the NCC-AC staff were required to make formal declarations of interest at the outset, and these were updated at every subsequent meeting throughout the development process. No interests were declared that required actions.

1.2 Declarations of interests of the GDG members

1.2.1 Ms Cecilia Fenerty

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She declared a personal pecuniary interest: she is a glaucoma speciality ophthalmic consultant working for the NHS with a subspecialty interest in glaucoma. She declared two non-personal pecuniary interests: her place of work, Manchester Royal Eye Hospital, received an award from Allergan in 2006 for £2500. She also received a Pfizer grant for research into persistence with glaucoma therapy (this research was not product specific). She declared no personal family interests or personal non-pecuniary interests.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	The declarations above plus: She declared a non-personal pecuniary interest: she received a donation of drop aids from Alcon for a study into compliance. This device is product specific as it can only be used with Travatan/Duotrav. The trial itself was not funded by Alcon.
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.2 Ms Wendy Franks

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She declared a personal pecuniary interest: she is a glaucoma specialist employed by Moorfields Eye Hospital NHS Trust and undertakes work in private practice. She declared a non-personal pecuniary interest: she received sponsorship for studies from Alcon, Allergan and Pfizer in her capacity as Director of Glaucoma contract research, a post she relinquished upon joining the GDG. She declared a personal non-pecuniary interest: she has published papers about her views of effectiveness of medical treatments. She declared no personal family interests.
Second GDG Meeting **(25th June 2007)**	She did not attend this meeting.
Third GDG Meeting **(26th July 2007)**	The declarations above plus: She declared a non-personal pecuniary interest: her department has received grants from the pharmaceutical industry.
Fourth GDG Meeting **(11th September 2007)**	She did not attend this meeting.
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	She did not attend this meeting.
Seventh GDG Meeting **(29th January 2008)**	The declarations above plus: She declared a personal pecuniary interest: she received an honorarium of €2000 covering travel/subsistence expenses to speak at the Rotterdam Glaucoma Club in January 2008. The lectures were not related to any company products. The meeting had sponsorship from Alcon.
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.3 Ms Mary Freeman

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She did not attend this meeting.
Second GDG Meeting **(25th June 2007)**	She declared a personal pecuniary interest: she received an honorarium from Novartis for speaking at an annual nurse symposium on age related macular degeneration in 2006 and 2007. Novartis also supported the attendance of an annual international conference in September '06 on "Advances in Wet AMD" by providing reasonable accommodation and travel expenses. Alcon supported the attendance of a meeting for specialist nurses on glaucoma by providing reasonable mileage cost and overnight accommodation in Hemel Hempstead. She sees NHS glaucoma patients. She declared no personal family interest, non-personal pecuniary interest, or personal non-pecuniary interest.
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	The declarations above plus: She declared a non-personal pecuniary interest: she is a study co-ordinator for a phase 3 trial using Macugen for diabetic maculopathy supported by Pfizer.
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	The declarations above plus: She declared a personal pecuniary interest: She was invited to speak at the annual Nurse symposium 2008 sponsored by Novartis on AMD. She accepted reasonable hospitality (overnight accommodation and transport). She declined an honorarium which was instead made payable to a hospital charitable fund. Post meeting she declared a personal non-pecuniary interest: She has had an article accepted for publication in Eye News on the glaucoma referral scheme in Sheffield. Due for publication Oct/Nov 08. She declared two personal pecuniary interests: She has also been invited to chair and speak at an educational meeting on glaucoma for nurses in Doncaster in November 08 sponsored by Allergan. She declined an honorarium and her speaker fees will be paid to the Trust. She has also invited to speak at the Royal College of Nursing (RCN) conference on the glaucoma referral scheme in Sheffield in September 08 for which she accepted reasonable overnight accommodation and transport cost reimbursement.

1.2.4 Mr Dennis Keight

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared a personal pecuniary interest: he owns shares in Astrazeneca and his pension is paid by Astrazeneca. Astrazeneca do not manufacture any drugs within this guideline. He declared a personal family interest: his wife is employed by Western Cheshire PCT as an IT project manager. His wife also acts as a consultant for Informing Healthcare (Wales) as a Health Data Consultant. He declared a personal non-pecuniary interest: he is a member of the International Glaucoma Association. He declared no non-personal pecuniary interest.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	He did not attend this meeting.
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	He amended his personal family interest: His wife is no longer employed directly by Western Cheshire PCT but occasionally undertakes consultancy work for them.
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.5 Ms Susana Ramirez-Florez

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She declared two non-personal pecuniary interests: She is an NHS Consultant Ophthalmologist and also undertakes work in private practice. Additionally the Department of Health, through the modernisation agency awarded Peterborough District Hospital, where she is employed, a grant of £422000 for the Glaucoma Community Optometrist Project. She declared no personal family interests or personal non-pecuniary interests.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	The declarations above plus: She declared a non-personal pecuniary interest: she took part in a visual field workshop for ophthalmic doctors in Peterborough which were sponsored by Allergan.
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	The declarations above plus: She declared two non-personal pecuniary interests: Peterborough & Stamford NHS Foundation Trust, her employer, distributed 60 posters designed by the Glaucoma Alliance Group lead by the RNIB to GP practices which were printed by Allergan, Alcon and Pfizer. After prior approval from NICE she was nominated for an award from Allergan, and was given travel expenses and accommodation to the venue after the Annual Ophthalmological Congress in Liverpool.
Ninth GDG Meeting **(25th April 2008)**	The declarations above plus: She declared a non-personal pecuniary interest: Her place of work is a pilot site for the Sibling Awareness Project led by the RNIB.
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	The declarations above plus: She declared a personal non-pecuniary interest: she was invited to a Merck Sharp and Dohme glaucoma meeting on 2 November 2008.
Twelfth GDG Meeting **(9th July 2008)**	The declarations above plus: She declared a non-personal pecuniary interest: Peterborough & Stamford NHS Foundation Trust was awarded 3rd place in the recent Allergan glaucoma awards and the prize of £3,000 will be spent on equipment for glaucoma care.
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.6 Ms Safina Rashid

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She did not attend this meeting.
Second GDG Meeting **(25th June 2007)**	She declared a personal pecuniary interest: she is an NHS employee. She declared no personal family interest, non-personal pecuniary interest, or personal non-pecuniary interest.
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	She did not attend this meeting.
Fifth GDG Meeting **(24th October 2007)**	The declarations above plus: She declared a personal pecuniary interest: she is the NHS Chair for BIOS (British and Irish Orthoptic Society).
Sixth GDG Meeting **(5th December 2007)**	She did not attend this meeting.
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	The declarations above plus: She declared a non-personal pecuniary interest: she led a teaching programme for nurses and optometrists which was sponsored by Pfizer via a £400 donation to the departmental research fund.
Eleventh GDG Meeting **(3rd June 2008)**	She did not attend this meeting.
Twelfth GDG Meeting **(9th July 2008)**	She did not attend this meeting.
Thirteenth GDG Meeting **(31st July 2008)**	She did not attend this meeting

1.2.7 Mr John Sparrow

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared a personal pecuniary interest: he is an NHS employee caring for glaucoma patients. He is a member of a limited liability partnership, the Consultant Eye Surgeons Partnership which delivers both NHS and private work although he does not undertake work in private practice. He declared two non-personal pecuniary interests: he was previously a primary investigator in the UK Glaucoma Treatment Study (UKGTS), a RCT of treatment for early glaucoma vs placebo. Funding for this study came through Moorfields Eye Hospital R&D department but originally was a grant from a drug company. In May 2007, he resigned as a PI at the study steering group meeting. Additionally he was previously a member of a research group investigating opacification of a particular lens implant (Hydroview H60M) used for cataract surgery. A grant from the lens manufacturer (Bausch & Lomb) now supports work looking into the extent and nature of this problem with recall of the patients who received this lens implant in Bristol. In May 2007, he resigned as an investigator on this study. He declared no personal family interests or personal non-pecuniary interests.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	He did not attend this meeting.
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.8 Mr Paul Spry

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared the following personal pecuniary interests: he owns shares in Healthcare Locums. He is also Editor-in-chief of the Optometric Glaucoma Society E-Journal, the production of which is sponsored by Pfizer. He is Chair of the College of Optometrists Glaucoma Panel. He declared a personal family interest: his wife works for Somerset PCT as a pharmacist medicines manager. He declared a non-personal pecuniary interest: he is a member of the steering committee for the United Kingdom Glaucoma treatment study. This study is funded by Pfizer. He declared no personal non-pecuniary interests.
Second GDG Meeting **(25th June 2007)**	He did not attend this meeting.
Third GDG Meeting **(26th July 2007)**	He did not attend this meeting.
Fourth GDG Meeting **(11th September 2007)**	He did not attend this meeting.
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	The declarations above plus: He declared two personal pecuniary interests: he works for New Medica which is an extended contractor for glaucoma care to NHS. He also received expenses for accommodation and transport costs to a conference on shared care from Allergan. His honorarium was donated to the Bristol Eye Hospital charitable trust.
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.9 Mr Chris Steele

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared a personal pecuniary interest: he is an NHS employee caring for glaucoma patients. He declared no personal family interest, non-personal pecuniary interest or personal non-pecuniary interest.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	He did not attend this meeting.
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	He did not attend this meeting.

1.2.10 Ms Sheila Urquhart

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	She declared a personal pecuniary interest: she was employed by Peterborough PCT as Clinical Governance Optometry Lead. She declared no personal family interest, non-personal pecuniary interest or personal non-pecuniary interest.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	No change to declarations
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	No change to declarations
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	No change to declarations
Eight GDG Meeting **(13th March 2008)**	She did not attend this meeting.
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	She declared that her personal pecuniary interest had expired: she is no longer Clinical Governance Optometry Lead for Peterborough PCT and so did not receive PCT funding after 30th April 2008
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.2.11 Mr Richard Wormald

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared a personal pecuniary interest: he is an NHS employee caring for glaucoma patients. He also undertakes work in private practice. He declared a non-personal non-pecuniary interest: he is on the steering committee for the UK Glaucoma Treatment Trial which is a study sponsored by Pfizer.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	The declarations above plus: He declared a personal non-pecuniary interest: he has been asked to speak at the Closed Meeting of the European Glaucoma Society on the deliberations of the NICE GDG
Fourth GDG Meeting **(11th September 2007)**	The declarations above plus: He declared a personal pecuniary interest: he received a fee from Merck Sharp and Dohme for £400 for running Saturday workshop on research methods for residents. He declared two non-personal pecuniary interests: He is investigator for the UK Glaucoma Treatment Trial and co-investigator for a compliance study at St Georges both of which are funded by Pfizer. He declared a personal non-pecuniary interest: he was invited to join the UK Glaucoma Alliance.
Fifth GDG Meeting **(24th October 2007)**	The declarations above plus: He declared a personal pecuniary interest: he received accommodation and travel expenses for a meeting in Durham on glaucoma funded by Alcon.
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	The declarations above plus: He declared a personal pecuniary interest: he spoke at a Merck Sharp and Dohme funded meeting and donated his fees to glaucoma department at Moorfields Eye Hospital.
Eight GDG Meeting **(13th March 2008)**	No change to declarations
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	He declared a personal pecuniary interest, expenses and honorarium for visit to University of Ottawa a visiting professor.
Eleventh GDG Meeting **(3rd June 2008)**	He did not attend this meeting.
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	The declarations above plus: He declared a personal pecuniary interest: he is chairing a clinical trials workshop in September 2008 which is sponsored by ACCO who in turn is funded by Allergan, his travel and accommodation expenses will be paid for.

1.2.12 Mr David Wright

GDG meeting	Declaration of Interests
First GDG meeting **(4th June 2007)**	He declared two personal pecuniary interests: as well as being a salaried employee of the International Glaucoma Association he is paid honoraria from Allergan, Pfizer, Alcon and Merck Sharp and Dohme, on an occasional basis for giving independent patients' perspective presentations. He declared a non-personal pecuniary interest: the International Glaucoma Association, his employer, receives funding for publications from Allergan, Alcon and Pfizer. Allergan has part funded a nurse employed by the IGA. He declared a personal non-pecuniary interest: he is a member of the UK Glaucoma Alliance, World Patient Association Eye Health programme. He declared no personal family interests.
Second GDG Meeting **(25th June 2007)**	No change to declarations
Third GDG Meeting **(26th July 2007)**	He did not attend this meeting.
Fourth GDG Meeting **(11th September 2007)**	No change to declarations
Fifth GDG Meeting **(24th October 2007)**	The declarations above plus: He declared a non-personal pecuniary interest: he received an honorarium worth £1500 from Pfizer for the All Eyes on Glaucoma Programme.
Sixth GDG Meeting **(5th December 2007)**	No change to declarations
Seventh GDG Meeting **(29th January 2008)**	He did not attend this meeting.
Eight GDG Meeting **(13th March 2008)**	He did not attend this meeting.
Ninth GDG Meeting **(25th April 2008)**	No change to declarations
Tenth GDG Meeting **(19th May 2008)**	No change to declarations
Eleventh GDG Meeting **(3rd June 2008)**	No change to declarations
Twelfth GDG Meeting **(9th July 2008)**	No change to declarations
Thirteenth GDG Meeting **(31st July 2008)**	No change to declarations

1.3 Declarations of interests of the NCC-AC members

GDG meeting	Declaration of Interests of the NCC-AC members
First GDG meeting **(4th June 2007)**	None
Second GDG Meeting **(25th June 2007)**	None
Third GDG Meeting **(26th July 2007)**	None
Fourth GDG Meeting **(11th September 2007)**	None
Fifth GDG Meeting **(24th October 2007)**	None
Sixth GDG Meeting **(5th December 2007)**	None
Seventh GDG Meeting **(29th January 2008)**	None
Eight GDG Meeting **(13th March 2008)**	None
Ninth GDG Meeting **(25th April 2008)**	None
Tenth GDG Meeting **(19th May 2008)**	None
Eleventh GDG Meeting **(3rd June 2008)**	None
Twelfth GDG Meeting **(9th July 2008)**	None
Thirteenth GDG Meeting **(31st July 2008)**	None

Appendix C

Search Strategies

Overview of Search Strategies

Searches were constructed by using the groups of terms listed below. These groups are expanded in full in the section on **Search Terms** following this.

Clinical searches were conducted in the following databases: Medline and Embase for all searches; The Cochrane Library (Central Register of Controlled Trials) for all searches excluding adverse events, risk factors and progression searches; Cinahl excluding laser and surgical treatments, additionally we did not have access to Cinahl when we ran the gonioscopy search; PsychINFO for patient education and information for patients; AMED (Allied and Complementary Medicine Database) for the complementary and alternative interventions; The Cochrane Database of Systematic Reviews and the Health Technology Assessment Database were searched for anything relating to glaucoma.

Economic searches were conducted in Medline, Embase, NHS EED (NHS Economic Evaluation Database) and HEED (Health Economic Evaluations Database). The HTA (Health Technology Assessment) database was also searched.

Adverse events – medications

Glaucoma/OHT terms
AND
Drugs intervention terms
AND
Adverse event terms
NOT
Animal/Publications filter

Complementary therapy

Simplified glaucoma/OHT terms
AND
Complementary therapy terms
AND
RCT filter or systematic review filter
NOT
Animal/Publications filter

Diagnosis searches

Glaucoma/OHT terms
AND
Diagnostic test terms
NOT
Animal/Publications filter

Economic searches

Glaucoma/OHT terms

AND
Intervention terms (Drugs/Surgery/Laser)
AND
Economic filter
NOT
Animal/Publications filter

Gonioscopy

Gonioscopy complete search provided below

Intervention searches

Glaucoma/OHT terms
AND
Intervention terms (Drugs/Surgery/Laser)
AND
RCT filter or systematic review filter
NOT
Animal/Publications filter

Monitoring

Simplified glaucoma/OHT terms
AND
Monitoring terms
NOT
Animal/Publications filter

Patient education

Glaucoma/OHT terms
AND
Patient education terms
NOT
Animal/Publications filter

Patient views

Glaucoma/OHT terms
AND
Patient view terms

Pigmentary dispersion syndrome

Pigmentary dispersion syndrome terms
AND
RCT filter
NOT
Animal/Publications filter

Progression searches

1.IOP-Glaucoma association complete search provided below
2. Progression from OHT to glaucoma complete search provided below

Quality of life

Glaucoma/OHT terms
AND
Quality of life terms
NOT
Animal/Publications filter

Risk factors

Risk factors complete search provided below

Service provision

Simplified glaucoma/OHT terms
AND
Service provision terms
NOT
Animal/Publications filter

Search terms

Adverse event terms

Adverse event terms Medline (OVID platform)

1 (ae or co or po or to or de).fs.

2 (safe or safety or side effect$ or undesirable effect$ or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.

3 risk$.mp. or exp cohort studies/ or between group:.tw.

4 1 or 2 or 3

Adverse event terms Embase (OVID platform)

1 (ae or co or po or to or de).fs.

2 (safe or safety or side effect$ or undesirable effect$ or tolerability or toxicity or adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.

3 risk$.mp. or exp cohort studies/ or between group:.tw.

4 1 or 2 or 3

Adverse events complete search Cinahl (Dialog/Datastar interface)

1 nonexperimental-studies#.de.

2 (confidence adj intervals).sh. or (funding adj source).sh.

3 1 or 2

Animal/Publication filter

Animal/publication Medline (OVID platform)

1 (Case-Reports NOT Randomized-Controlled-Trial OR Letter OR Historical-Article OR Review-Of-Reported-Cases).PT. OR (exp Animals/ NOT Humans/)

Animal/publication filter Embase (OVID platform)

1 Case-Study/ or Abstract-Report/ or Letter/ or (case adj report).tw. or ((exp Animal/ or Nonhuman/ or exp Animal-Experiment/) not exp Human/)

Complementary therapy terms

Complementary therapy terms Medline (OVID platform)

1 exp Complementary Therapies/ or (herbal remed$ or homeopath$).tw.
2 Ginkgo biloba/ or ginkgo biloba.tw.
3 exp vitamins/ or (vitamin$ or multivitamin$ or megavitamin$ or mega-vitamin or multi-vitamin).tw.
4 (therapeutic touch or (touch adj5 (therap$ or heal$ or treat$)) or ((energy based or energy-based) and (therap$ or heal$ or treat$)) or energy healing or Reiki).tw.
5 exercise therapy/ or exercise.tw.
6 diet therapy/ or special diet.tw.
7 Osteopathic medicine/ or exp Musculoskeletal manipulation/ or spinal manipulation.tw.
8 (meditation or relaxation).tw.
9 cannabis/ or cannabinoids/ or (cannabis or marijuana).tw.
10 neuroprotective agents/ or memantine/ or (neuroprotective agent$ or neuroprotection or memantine).tw.
11 exp acupuncture therapy/ or acupuncture.tw.
12 or/1-11

Complementary therapy terms Embase (OVID platform)

1 exp alternative medicine/ or (herbal remed$ or homeopath$).tw.
2 ginkgo biloba/ or ginkgo biloba.tw.
3 exp vitamin/ or (vitamin$ or multivitamin$ or megavitamin$ or multi-vitamin$ or mega-vitamin$).tw.
4 (therapeutic touch or (touch adj5 (therap$ or heal$ or treat$)) or ((energy based or energy-based) and (therap$ or heal$ or treat$)) or energy healing or Reiki).tw.
5 exercise therapy/ or exercise.tw.
6 diet therapy/ or special diet.tw.
7 Osteopathic medicine/ or Manipulative medicine/ or spinal manipulation.tw.
8 (meditation or relaxation).tw.
9 Cannabis/ or cannabinoids/ or (cannabis or marijuana).tw.
10 Neuroprotection/ or memantine/ or (neuroprotective agent$ or neuroprotection or memantine).tw.
11 Acupuncture/ or acupuncture.tw.
12 or/1-11

Complementary therapy terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Complementary Therapies explode all trees

2 herbal remed* or homeopath*

3 MeSH descriptor Ginkgo biloba, this term only

4 ginkgo biloba

5 MeSH descriptor Vitamins explode all trees

6 vitamin* or multivitamin* or megavitamin* or mega-vitamin or multi-vitamin

7 (therapeutic touch or (touch near (therap* or heal* or treat*)) or ((energy based or energy-based) and (therap* or heal* or treat*)) or energy healing or Reiki)

8 MeSH descriptor Exercise Therapy explode all trees

9 exercise

10 MeSH descriptor Diet Therapy, this term only

11 special diet

12 spinal manipulation

13 meditation or relaxation

14 MeSH descriptor Cannabis, this term only

15 MeSH descriptor Cannabinoids, this term only

16 cannabis or marijuana

17 MeSH descriptor Neuroprotective Agents explode all trees

18 MeSH descriptor Memantine, this term only

19 neuroprotective agent* or neuroprotection or memantine

20 MeSH descriptor Acupuncture, this term only

21 acupuncture

22 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21

Complementary therapy terms Cinahl (NLH Search 2.0 interface)

1 ALTERNATIVE THERAPIES/ OR (herbal remed* OR homeopath*)

2 GINKGO BILOBA/ OR ginkgo biloba

3 exp VITAMINS/ OR vitamin* OR multivitamin* OR megavitamin* OR mega-vitamin OR multi-vitamin

4 (therapeutic AND touch OR (touch AND (therap* OR heal* OR treat*)) OR ((energy based OR energy-based) AND (therap* OR heal* OR treat*)) OR energy AND healing OR Reiki).af

5 EXERCISE/ OR THERAPEUTIC EXERCISE/ OR exercise

6 DIET THERAPY/ OR SPECIAL DIET/ OR special diet

7 OSTEOPATHIC MEDICINE/ OR exp MUSCULOSKELETAL MANIPULATION/ OR spinal manipulation

8 (meditation OR relaxation).af

9 CANNABIS/ OR CANNABINOIDS/ OR cannabis OR marijuana

10 NEUROPROTECTIVE AGENTS/ OR MEMANTINE/ OR neuroprotective agent* OR neuroprotection OR memantine

11 exp ACUPUNCTURE THERAPY/ OR acupuncture

12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

Complementary therapy terms Amed (NLH Search 2.0 interface)

1 COMPLEMENTARY MEDICINE/ OR COMPLEMENTARY THERAPIES/ OR (herbal remed* OR homeopath*)

2 GINKGO BILOBA/ OR ginkgo biloba

3 exp VITAMINS/ OR vitamin* OR multivitamin* OR megavitamin* OR mega-vitamin OR multi-vitamin

4 (therapeutic AND touch OR (touch AND (therap* OR heal* OR treat*)) OR ((energy AND based OR energy-based) AND (therap* OR heal* OR treat*)) OR energy AND healing OR Reiki).af

5 EXERCISE/ OR exercise

6 (special AND diet).ti,ab

7 OSTEOPATHY/ OR spinal manipulation

8 MEDITATION/ OR RELAXATION/ OR (meditation OR relaxation).af

9 CANNABIS/ OR CANNABINOIDS/ OR cannabis OR marijuana

10 neuroprotective agent* OR neuroprotection OR memantine

11 ACUPUNCTURE/ OR acupuncture

12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

Diagnostic test terms

Diagnostic test terms Medline (OVID platform)

1 exp Perimetry/

2 (Visual field exam$ or visual field test or SITA or Humphrey or Swedish interactive testing algorithm or Henson or ((threshold or supra threshold or supra-threshold) adj3 perimetry)).tw.

3 exp Tonometry, Ocular/

4 (Tonomet$ or applanation or tonopen or pneumotonometry or Perkins or Goldmann or pulse air).tw.

5 exp tomography, optical coherence/ or exp tomography, optical/ or exp ophthalmoscopy/

6 (((stereo or digital or optic nerve head) adj3 photograph$) or Heidelberg or ((scanning or laser) adj3 ophthalmoscop$) or optical coherence tomography or polarimetry or nerve fiber analys$ or nerve fibre analys$ or Octopus or frequency doubling technology or Armaly).tw.

7 or/1-6

Diagnostic test terms Embase (OVID platform)

1 Perimetry/

2 (Visual field exam$ or visual field test or SITA or Humphrey or Swedish interactive testing algorithm or Henson or ((threshold or supra threshold or supra-threshold) adj3 perimetry)).tw.

3 Tonometry, Ocular/

4 (Tonomet$ or applanation or tonopen or pneumotonometry or Perkins or Goldmann or pulse air).tw.

5 exp tomography, exp optical coherence/ or tomography, optical/ or ophthalmoscopy/ or scanning laser ophthalmoscopy/

6 (((stereo or digital or optic nerve head) adj3 photograph$) or Heidelberg or ((scanning or laser) adj3 ophthalmoscop$) or optical coherence tomography or polarimetry or nerve fiber analys$ or nerve fibre analys$ or Octopus or frequency doubling technology or Armaly).tw.

7 or/1-6

Diagnostic test terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Perimetry explode all trees

2 (Visual field exam* or visual field test or SITA or Humphrey or Swedish interactive testing algorithm or Henson or ((threshold or supra threshold or supra-threshold) near perimetry))

3 MeSH descriptor Tonometry, Ocular explode all trees

4 (Tonomet* or applanation or tonopen or pneumotonometry or Perkins or Goldmann or pulse air)

5 MeSH descriptor Tomography, Optical explode all trees

6 MeSH descriptor Tomography, Optical Coherence explode all trees

7 MeSH descriptor Ophthalmoscopy explode all trees

8 (((stereo or digital or optic nerve head) near photograph*) or Heidelberg or ((scanning or laser) near ophthalmoscop*) or optical coherence tomography or polarimetry or nerve fiber analys* or nerve fibre analys* or Octopus or frequency doubling technology or Armaly)

9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

Diagnostic test terms Cinahl (NLH Search 2.0 interface)

1 exp PERIMETRY/

2 (Visual AND field AND exam* OR visual AND field AND test OR SITA OR Humphrey OR Swedish AND interactive AND testing AND algorithm OR Henson OR ((threshold OR supra threshold OR supra-threshold) AND perimetry)).ti,ab

3 exp TONOMETRY/

4 (Tonomet* OR applanation OR tonopen OR pneumotonometry OR Perkins OR Goldmann OR pulse AND air).ti,ab

5 exp OPHTHALMOSCOPY/

6 (((stereo OR digital OR optic nerve head) AND photograph*) OR Heidelberg OR ((scanning OR laser) AND ophthalmoscop*) OR optical AND coherence AND tomography OR polarimetry OR nerve AND fiber AND analys* OR nerve AND fibre AND analys* OR Octopus OR frequency AND doubling AND technology OR Armaly).ti,ab

7 1 or 2 or 3 or 4 or 5 or 6

Economic filter

Economic filter (including quality of life terms) Medline (OVID platform)

1 exp "Costs and Cost Analysis"/

2 Economics/

3 exp Economics, Nursing/ or exp Economics, Medical/ or Economics/ or exp Economics, Hospital/ or exp Economics, Pharmaceutical/

4 exp "Fees and Charges"/

5 exp Budgets/

6 budget$.tw.

7 cost$.tw.

8 (economic$ or pharmacoeconomic$ or pharmaco-economic$).tw.

9 (price$ or pricing$).tw.

10 (financial or finance or finances or financed).tw.

11 (fee or fees).tw.

12 (value adj2 (money or monetary)).tw.

13 ec.fs.

14 exp Resource Allocation/

15 resourc$ allocat$.tw.

16 expenditure$.tw.

17 (fund or funds or funding or fundings or funded).tw.

18 (ration or rations or rationing or rationings or rationed).tw.

19 (saving or savings).tw.

20 or/1-19

21 exp "Quality of Life"/

22 quality of life.tw.

23 life quality.tw.

24 Value of Life/

25 quality adjusted life.tw.

26 (qaly$ or qald$ or qale$ or qtime$).tw.

27 disability adjusted life.tw.

28 daly$.tw.

29 exp Health Status Indicators/

30 health status.tw.

31 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

32 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

33 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

34 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

35 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

36 (euroqol or euro qol or eq5d or eq 5d).tw.

37 (hql or hqol or h qol or hrqol or hr qol).tw.

38 (hye or hyes).tw.

39 health$ equivalent$ year$.tw.

40 (hui or hui1 or hui2 or hui3).tw.

41 utilit$.tw.

42 disutilit$.tw.

43 rosser.tw.

44 quality of wellbeing.tw.

45 qwb.tw.

46 willingness to pay.tw.

47 standard gamble$.tw.

48 time trade off.tw.

49 time tradeoff.tw.

50 tto.tw.

51 factor analy$.tw.

52 preference based.tw.

53 (state adj2 valu$).tw.

54 Life Expectancy/

55 life expectancy$.tw.

56 ((duration or length or period of time or lasting or last or lasted) adj4 symptom$).tw.

57 or/21-56

58 exp models, economic/

59 models, theoretical/ or models, organizational/

60 markov chains/

61 markov$.tw.

62 Monte Carlo Method/

63 monte carlo.tw.

64 exp Decision Theory/

65 (decision$ adj2 (tree$ or analy$ or model$)).tw.

66 exp models, statistical/

67 model$.tw.

68 or/58-67

69 20 or 57 or 68

Economic filter (including quality of life terms) Embase (OVID platform)

1 exp economic aspect/

2 cost$.tw.

3 (price$ or pricing$).tw.

4 (fee or fees).tw.

5 (financial or finance or finances or financed).tw.

6 (value adj2 (money or monetary)).tw.

7 resourc$ allocat$.tw.

8 expenditure$.tw.

9 (fund or funds or funding or fundings or funded).tw.

10 (ration or rations or rationing or rationings or rationed).tw.

11 (saving or savings).tw.

12 or/1-11

13 Quality of Life/

14 quality of life.tw.

15 life quality.tw.

16 quality adjusted life.tw.

17 (qaly$ or qald$ or qale$ or qtime$).tw.

18 disability adjusted life.tw.

19 daly$.tw.

20 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

21 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

22 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

23 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

24 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

25 (euroqol or euro qol or eq5d or eq 5d).tw.

26 (hql or hqol or h qol or hrqol or hr qol).tw.

27 (hye or hyes).tw.

28 health$ equivalent$ year$.tw.

29 (hui or hui1 or hui2 or hui3).tw.

30 health utilit$.tw.

31 disutilit$.tw.

32 rosser.tw.
33 (quality of wellbeing or quality of well being).tw.
34 qwb.tw.
35 willingness to pay.tw.
36 standard gamble$.tw.
37 time trade off.tw.
38 time tradeoff.tw.
39 tto.tw.
40 factor analy$.tw.
41 preference based.tw.
42 (state adj2 valu$).tw.
43 Life Expectancy/
44 life expectancy$.tw.
45 ((duration or length or period of time or lasting or last or lasted) adj4 symptom$).tw.
46 or/13-46
47 exp model/
48 exp Mathematical Model/
49 markov$.tw.
50 Monte Carlo Method/
51 monte carlo.tw.
52 exp Decision Theory/
53 (decision$ adj2 (tree$ or anlay$ or model$)).tw.
54 model$.tw.
55 or/47-55
56 12 or 46 or 55

COAG/OHT terms

COAG/OHT terms Medline (OVID platform)

1 Ocular Hypertension/
2 ((increas$ or elevat$ or high$) adj3 (ocular or intraocular or intra-ocular) adj3 pressure).tw.
3 ocular hypertension.tw.
4 exp Glaucoma, Open-Angle/
5 (open adj5 angle adj5 glaucom$).tw.
6 ((low or normal or sine) adj5 (tension or pressure) adj5 glaucom$).tw.
7 (poag or oht or ntg or npg).tw.
8 ((primary or chronic or exfoliat$ or pseudo-exfoliat$ or pseudo exfoliat$ or pseudoexfoliat$ or pigment$) adj5 glaucom$).tw.
9 or/1-8

COAG/OHT terms Embase (OVID platform)

1 Intraocular Hypertension/

2 ((increas$ or elevat$ or high$ or raise$) adj3 (ocular or intraocular or intra-ocular) adj3 pressure).tw.

3 ocular hypertension.tw.

4 Open Angle Glaucoma/

5 Low Tension Glaucoma/

6 (open adj5 angle adj5 glaucom$).tw.

7 ((low or normal or sine) adj5 (tension or pressure) adj5 glaucom$).tw.

8 (poag or oht or ntg or npg).tw.

9 ((primary or chronic or exfoliat$ or pseudo-exfoliat$ or pseudo exfoliat$ or pseudoexfoliat$ or pigment$) adj5 glaucom$).tw.

10 or/1-9

COAG/OHT terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Ocular Hypertension, this term only

2 ((increas* or elevat* or high* or raise*) near (ocular or intraocular or intra-ocular) near pressure)

3 ocular hypertension

4 MeSH descriptor Glaucoma, Open-Angle

5 (open near angle near glaucom*)

6 ((low or normal or sine) near (tension or pressure) near glaucom*)

7 (poag or oht or ntg or npg)

8 ((primary or chronic or exfoliat* or pseudo-exfoliat* or pseudo exfoliat* or pseudoexfoliat* or pigment*) near glaucom*)

9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

COAG/OHT terms Cinahl (NLH Search 2.0 interface)

1 OCULAR HYPERTENSION/

2 (ocular AND hypertension).ti,ab

3 GLAUCOMA/

4 1 or 2 or 3

COAG/OHT terms PsycINFO (NLH Search 2.0 interface)

1 GLAUCOMA/

2 glaucoma.ti,ab

3 (intraocular AND pressure OR intraocular AND tension).ti,ab

4 1 or 2 or 3

Gonioscopy complete search

Gonioscopy complete search Medline (OVID platform)

1 Glaucoma/
2 exp Glaucoma, Open-Angle/
3 glaucoma$.tw.
4 Ocular Hypertension/
5 ((increas$ or elevat$ or high$ or raise$) adj3 (ocular or intraocular or intra-ocular) adj3 pressure).tw.
6 ocular hypertension.tw.
7 (poag or oht or ntg or npg).tw.
8 or/1-7
9 Gonioscopy/
10 gonioscop$.tw.
11 or/9-10
12 animal/ not human/
13 (comment or letter or editorial or case reports).pt.
14 12 or 13
15 (8 and 11) not 14

Gonioscopy complete search Embase (OVID platform)

1 Glaucoma/
2 Open Angle Glaucoma/
3 Low Tension Glaucoma/
4 glaucoma$.tw.
5 Intraocular Hypertension/
6 ((increas$ or elevat$ or high$ or raise$) adj3 (ocular or intraocular or intra-ocular) adj3 pressure).tw.
7 ocular hypertension.tw.
8 (poag or oht or ntg or npg).tw.
9 or/1-8
10 Gonioscopy/
11 gonioscop$.tw.
12 or/10-11
13 (exp Animal/ or Nonhuman/ or exp Animal-Experiment/) not exp Human/
14 Case-Study/ or Abstract-Report/ or Letter/ or (case adj report).tw.
15 13 or 14
16 (9 and 12) not 15

Gonioscopy complete search The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Gonioscopy, this term only
2 gonioscop*

3 #1 or #2

Medication intervention terms

Medication intervention terms Medline (OVID platform)

1 exp Drug Therapy/

2 exp Antihypertensive Agents/

3 exp adrenergic beta-antagonists/

4 (beta-blocker$ or betablocker$ or timolol or carteolol or betaxolol or levobunolol or befunolol or metipranolol or teoptic or betagan or optipranolol).mp.

5 (prostaglandin$ or bimatoprost or latanoprost or travoprost or unoprostone or lumigan or xalatan or travatan).mp.

6 (carbonic anhydrase inhibitor$ or dorzolamid$ or brinzolamid$ or acetazolamide or azopt or trusopt or diamox).mp.

7 (sympathomimetic$ or brimonidin$ or apraclonidin$ or clonidin$ or dipivefrin$).mp.

8 (miotic$ or pilocarpin$).mp.

9 or/1-8

Medication intervention terms Embase (OVID platform)

1 exp Drug Therapy/

2 exp Antihypertensive Agents/

3 exp Antiglaucoma Agent/

4 exp Beta Adrenergic Receptor Blocking Agent/

5 (beta-blocker$ or betablocker$ or timolol or carteolol or betaxolol or levobunolol or befunolol or metipranolol or teoptic or betagan or optipranolol).mp.

6 (prostaglandin$ or bimatoprost or latanoprost or travoprost or unoprostone or lumigan or xalatan or travatan).mp.

7 (carbonic anhydrase inhibitor$ or dorzolamid$ or brinzolamid$ or acetazolamide or azopt or trusopt or diamox).mp.

8 (sympathomimetic$ or brimonidin$ or apraclonidin$ or clonidin$ or dipivefrin$).mp.

9 (miotic$ or pilocarpin$).mp.

10 or/1-9

Medication intervention terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Drug Therapy explode all trees

2 MeSH descriptor Antihypertensive Agents explode all trees

3 MeSH descriptor Adrenergic beta-Antagonists explode all trees

4 beta-blocker* or betablocker* or timolol or carteolol or betaxolol or levobunolol or befunolol or metipranolol or teoptic or betagan or optipranolol

5 prostaglandin* or bimatoprost or latanoprost or travoprost or unoprostone or lumigan or xalatan or travatan

6 carbonic anhydrase inhibitor* or dorzolamid* or brinzolamid* or acetazolamide or azopt or trusopt or diamox

7 sympathomimetic* or brimonidin* or apraclonidin* or clonidin* or dipivefrin*

8 miotic* or pilocarpin*

9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

Medication intervention terms Cinahl (NLH Search 2.0 interface)

1 exp DRUG THERAPY/

2 exp ANTIHYPERTENSIVE AGENTS/

3 (beta-blocker* OR betablocker* OR timolol OR carteolol OR betaxolol OR levobunolol OR befunolol OR metipranolol OR teoptic OR betagan OR optipranolol).af

4 (prostaglandin* OR bimatoprost OR latanoprost OR travoprost OR unoprostone OR lumigan OR xalatan OR travatan).af

5 (carbonic AND anhydrase AND inhibitor* OR dorzolamid* OR brinzolamid* OR acetazolamide OR azopt OR trusopt OR diamox).af

6 (sympathomimetic* OR brimonidin* OR apraclonidin* OR clonidin* OR dipivefrin*).af

7 (miotic* OR pilocarpin*).af

8 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7

Monitoring terms

Monitoring terms Medline/Embase (Ovid interface)

1 (review$ adj (interval$ or visit$ or inspect$ or examin$ or attend$ or check-up$ or recall$)).tw.

2 (routine$ adj (interval$ or visit$ or inspect$ or examin$ or attend$ or check-up$ or recall$)).tw.

3 (periodic$ adj (interval$ or visit$ or inspect$ or examin$ or attend$ or check-up$ or recall$)).tw.

4 (regular adj (visit$ or inspect$ or examin$ or attend$ or check-up$)).tw.

5 (recall$ adj interval$).tw.

6 (visit$ adj5 clinic$).tw.

7 or/1-6

Monitoring terms The Cochrane Library (Wiley Interscience interface)

1 (review* next (interval* or visit* or inspect* or examin* or attend* or check-up* or recall*))

2 (routine* next (interval* or visit* or inspect* or examin* or attend* or check-up* or recall*))

3 (periodic* next (interval* or visit* or inspect* or examin* or attend* or check-up* or recall*))

4 (regular next (visit* or inspect* or examin* or attend* or check-up*))

5 (recall* next interval*)

6 (visit* near clinic*).tw.

7 #1 or #2 or #3 or #4 or #5 or #6

Patient education terms

Patient education terms Medline (OVID platform)

1 Patients/ or Inpatients/ or Outpatients/

2 Caregivers/ or exp Family/ or exp Parents/ or exp Legal-Guardians/

3 (patients or carer$ or famil$).tw.

4 or/1-3

5 Popular-Works-Publication-Type/ or exp Information-Services/ or Publications/ or Books/ or Pamphlets/ or Counseling/ or Directive-Counseling/

6 4 and 5

7 ((patient or patients) adj3 (education or educate or educating or information or literature or leaflet$ or booklet$ or pamphlet$)).ti,ab.

8 Patient-Education/ or Patient-Education-Handout-Publication-Type/

9 or/6-8

Patient education terms Embase (OVID platform)

1 Patient/ or Hospital patient/ or Outpatient/

2 Caregiver/ or exp Family/ or exp Parent/

3 (patients or carer$ or famil$).tw.

4 or/1-3

5 Information Service/ or Information center/ or Publication/ or Book/ or Counseling/ or Directive counseling/

6 4 and 5

7 ((patient or patients) adj3 (education or educate or educating or information or literature or leaflet$ or booklet$ or pamphlet$)).ti,ab.

8 Patient information/ or Patient education/

9 or/6-8

Patient education terms Cinahl (NLH Search 2.0 interface)

1 PATIENTS/

2 INPATIENTS/

3 CAREGIVERS/

4 exp FAMILY/

5 exp PARENTS/

6 exp GUARDIANSHIP, LEGAL/

7 (patients OR carer* OR famil*).ti,ab

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 exp INFORMATION SERVICES/

10 BOOKS/

11 PAMPHLETS/

12 COUNSELING/

13 9 or 10 or 11 or 12

14 8 and 13

15 ((patient OR patients) AND (education OR educate OR educating OR information OR literature OR leaflet* OR booklet* OR pamphlet*)).ti,ab

16 PATIENT EDUCATION/

17 14 or 15 or 16

Patient education terms PsycINFO (NLH Search 2.0 interface)

1 PATIENTS/ OR MEDICAL PATIENTS/

2 OUTPATIENTS/

3 CAREGIVERS/

4 exp FAMILY/

5 exp PARENTS/

6 GUARDIANSHIP/

7 (patients OR carer* OR famil*).ti,ab

8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 exp INFORMATION SERVICES/

10 BOOKS/

11 COUNSELING/

12 9 or 10 or 11

13 8 and 13

14 ((patient OR patients) AND (education OR educate OR educating OR information OR literature OR leaflet* OR booklet* OR pamphlet*)).ti,ab

15 CLIENT EDUCATION/

16 HEALTH EDUCATION/

17 14 or 15 or 16

Patient view terms

Patient view terms Medline (OVID platform)

1 exp Consumer-Satisfaction/ or Personal-Satisfaction/ or exp Patient-Acceptance-Of-Health-Care/ or exp Consumer-Participation/ or exp Patient-Rights/ or Health Care Surveys/ or Questionnaires/ or Interview/ or Focus groups/

2 (patient$ adj3 (view$ or opinion$ or awareness or persistenc$ or attitude$ or compliance or satisfaction or concern$ or belief$ or feeling$ or position or idea$ or preference$ or choice$)).tw.

3 (Discomfort or comfort or inconvenience or bother or trouble or fear$ or anxiety or anxious).tw.

4 or/1-3

Patient view terms Embase (OVID platform)

1 Consumer attitude/ or patient satisfaction/ or patient compliance/ or patient right/ or health survey/ or questionnaire/ or interview/

2 (patient$ adj3 (view$ or opinion$ or awareness or persistenc$ or attitude$ or compliance or satisfaction or concern$ or belief$ or feeling$ or position or idea$ or preference$ or choice$)).tw.

3 (Discomfort or comfort or inconvenience or bother or trouble or fear$ or anxiety or anxious).tw.

4 or/1-3

Patient view terms Cinahl (NLH Search 2.0 interface)

1 PATIENT SATISFACTION/

2 CONSUMER SATISFACTION/ OR CONSUMER ATTITUDES/

3 PATIENT RIGHTS/

4 SURVEYS/

5 QUESTIONNAIRES/

6 FOCUS GROUPS/

7 INTERVIEWS/

8 ((patient* AND (view* OR opinion* OR awareness OR persistenc* OR attitude* OR compliance OR satisfaction OR concern* OR belief* OR feeling* OR position OR idea* OR preference* OR choice*))).ti,ab

9 (Discomfort OR comfort OR inconvenience OR bother OR trouble OR fear* OR anxiety OR anxious).ti,ab

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

Patient view terms PsycINFO (NLH Search 2.0 interface)

1 CONSUMER ATTITUDES/ OR CONSUMER SATISFACTION/ OR CONSUMER SURVEYS/

2 SURVEYS/

3 QUESTIONNAIRES/

4 INTERVIEWS/

5 ((patient* AND (view* OR opinion* OR awareness OR persistenc* OR attitude* OR compliance OR satisfaction OR concern* OR belief* OR feeling* OR position OR idea* OR preference* OR choice*))).ti,ab

6 (Discomfort OR comfort OR inconvenience OR bother OR trouble OR fear* OR anxiety OR anxious).ti,ab

7 1 or 2 or 3 or 4 or 5 or 6

Pigmentary dispersion syndrome terms

Pigmentary dispersion syndrome Medline/Embase (OVID platform)

1 pigment$ dispers$ syndrome.tw.

Pigmentary dispersion syndrome The Cochrane Library (Wiley Interscience interface)

1 pigment* dispers* syndrome

Progression terms

1. IOP-Glaucoma association complete search

Progression Medline (IOP-glaucoma association) (OVID platform)

1 Glaucoma/
2 Glaucoma, Open-Angle/
3 (open adj5 angle adj5 glaucom$).tw.
4 ((low or normal or sine) adj5 (tension or pressure) adj5 glaucom$).tw.
5 or/1-4
6 (visual field$ or optic disc$ or optic nerve$ or optic neuropathy$).mp.
7 ((intraocular or intra-ocular or ocular) adj pressure).mp.
8 exp regression analysis/
9 regression.tw.
10 disease progression/
11 progression.tw.
12 prognosis/
13 or/8-12
14 5 and 6 and 7 and 13

Progression Embase (IOP-glaucoma association) (OVID platform)

1 Glaucoma/
2 Open Angle Glaucoma/
3 Low Tension Glaucoma/
4 (open adj5 angle adj5 glaucom$).tw.
5 ((low or normal or sine) adj5 (tension or pressure) adj5 glaucom$).tw.
6 or/1-5
7 ((intraocular or intra-ocular or ocular) adj pressure).mp.
8 (visual field$ or optic disc$ or optic nerve$ or optic neuropathy$).mp.
9 exp regression analysis/
10 regression.tw.
11 disease course/
12 progression.tw.
13 prognosis/
14 or 9-13
15 6 and 7 and 8 and 14

2. Progression from OHT to glaucoma complete search

Progression 2 Medline (progression OHT to glaucoma) (OVID platform)

1 Glaucoma/
2 Glaucoma, Open-Angle/
3 glaucom$.tw.
4 or/1-3
5 Ocular Hypertension/
6 ((intraocular or ocular) adj hypertension).mp.
7 5 or 6
8 disease progression/
9 progression.tw.
10 conversion.tw.
11 prognosis/
12 or/8-11
13 4 and 7 and 12

Progression 2 Embase (progression OHT to glaucoma) (OVID platform)

1 Glaucoma/
2 Open Angle Glaucoma/
3 Low Tension Glaucoma/
4 glaucoma$.tw.
5 or/1-4
6 Intraocular Hypertension/
7 ((intraocular or ocular) adj hypertension).mp.
8 6 or 7
9 disease course/
10 progression.tw.
11 conversion.tw.
12 prognosis/
13 or/9-12
14 5 and 8 and 13

Quality of life terms

Quality of life terms Medline (OVID platform)

1 exp "Quality of Life"/
2 quality of life.tw.
3 life quality.tw.
4 Value of Life/
5 quality adjusted life.tw.

6 (qaly$ or qald$ or qale$ or qtime$).tw.

7 disability adjusted life.tw.

8 daly$.tw.

9 exp Health Status Indicators/

10 health status.tw.

11 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

12 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

13 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

14 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

15 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

16 (euroqol or euro qol or eq5d or eq 5d).tw.

17 (hql or hqol or h qol or hrqol or hr qol).tw.

18 (hye or hyes).tw.

19 health$ equivalent$ year$.tw.

20 (hui or hui1 or hui2 or hui3).tw.

21 utilit$.tw.

22 disutilit$.tw.

23 rosser.tw.

24 quality of wellbeing.tw.

25 qwb.tw.

26 willingness to pay.tw.

27 standard gamble$.tw.

28 time trade off.tw.

29 time tradeoff.tw.

30 tto.tw.

31 factor analy$.tw.

32 preference based.tw.

33 (state adj2 valu$).tw.

34 Life Expectancy/

35 life expectancy$.tw.

36 ((duration or length or period of time or lasting or last or lasted) adj4 symptom$).tw.

37 or/1-36

Quality of life terms Embase (OVID platform)

1 Quality of Life/

2 quality of life.tw.

3 life quality.tw.

4 quality adjusted life.tw.

5 (qaly$ or qald$ or qale$ or qtime$).tw.

6 disability adjusted life.tw.

7 daly$.tw.

8 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.

9 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

10 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.

11 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

12 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.

13 (euroqol or euro qol or eq5d or eq 5d).tw.

14 (hql or hqol or h qol or hrqol or hr qol).tw.

15 (hye or hyes).tw.

16 health$ equivalent$ year$.tw.

17 (hui or hui1 or hui2 or hui3).tw.

18 health utilit$.tw.

19 disutilit$.tw.

20 rosser.tw.

21 (quality of wellbeing or quality of well being).tw.

22 qwb.tw.

23 willingness to pay.tw.

24 standard gamble$.tw.

25 time trade off.tw.

26 time tradeoff.tw.

27 tto.tw.

28 factor analy$.tw.

29 preference based.tw.

30 (state adj2 valu$).tw.

31 Life Expectancy/

32 life expectancy$.tw.

33 ((duration or length or period of time or lasting or last or lasted) adj4 symptom$).tw.

34 or/1-33

Randomised controlled trial (RCT) filter

RCT filter Medline (OVID platform)

1 Randomized-Controlled-Trials/ or Random-Allocation/ or Double-Blind-Method/ or Single-Blind-Method/ or exp Clinical-Trials as topic/ or Cross-Over-Studies/ or Prospective-Studies/ or Placebos/

2 (Randomized-Controlled-Trial or Clinical-Trial or Controlled-Clinical-Trial).pt.

3 ((((((((((clinical or control or controlled) adj (study or trial)) or (single or double or triple)) adj (blind$3 or mask$3)) or randomised or randomized or random$) adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or crossover) adj (design or study or trial)) or placebo or placebos).ti,ab.

4 or/1-3

RCT filter Embase (OVID platform)

1 Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/

2 ((((((((((clinical or control or controlled) adj (study or trial)) or (single or double or triple)) adj (blind$3 or mask$3)) or randomised or randomized or random$) adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or crossover) adj (design or study or trial)) or placebo or placebos).ti,ab.

3 1 or 2

Risk factors complete search

Risk factors complete search Medline (OVID platform)

1 ocular hypertension/

2 ((ocular or intraocular) adj1 hypertension).tw.

3 1 or 2

4 exp Glaucoma, Open-Angle/ or Glaucoma/

5 (glaucoma or poag).tw.

6 4 or 5

7 3 and 6

8 prevalence/

9 incidence/

10 epidemiology/

11 Longitudinal Studies/

12 ((incidence or prevalence or epidemiol$) adj3 (glaucom$ or poag or vision or visual or blind$)).tw.

13 or/8-12

14 7 and 13

15 age factors/

16 aged/

17 middle aged/

18 elderly.tw.

19 exp population groups/

20 (race or racial).tw.

21 ethnic$.tw.

22 family history.tw.

23 (inherited or familial).tw.

24 myopia/

25 (myopia or myopic).tw.

26 ((short or near) adj2 sight$).tw.

27 (shortsight$ or nearsight$).tw.

28 exp Diabetes Mellitus, Type 2/

29 diabetes.tw.

30 ((exfoliat$ or pseudo-exfoliat$ or pseudo exfoliat$ or pseudoexfoliat$ or pigment$) adj5 (glaucom$ or syndrome or disorder)).tw.

31 pigment$ dispers$ syndrome.tw.

32 central corneal thickness.tw.

33 ((ocular or intraocular or intra-ocular) adj pressure).tw.

34 (cup adj2 disc adj1 ratio).tw.

35 (disc adj1 (haemorrhag$ or hemorrhag$ or bleed$)).tw.

36 or/15-35

37 7 and 36

38 exp risk/

39 causality/

40 Precipitating Factors/

41 prognosis/

42 (risk adj3 (stratif$ or assess$ or factor?)).tw.

43 (risk adj1 relative).tw.

44 (predict$ or prognosis or prognostic).tw.

45 cohort studies/

46 or/38-45

47 37 and 46

48 14 or 47

Risk factors complete search Embase (OVID platform)

1 Intraocular Hypertension/

2 ((ocular or intraocular) adj1 hypertension).tw.

3 1 or 2

4 exp OPEN ANGLE GLAUCOMA/ or GLAUCOMA/

5 (glaucoma or poag).tw.

6 4 or 5

7 3 and 6

8 PREVALENCE/

9 INCIDENCE/

10 EPIDEMIOLOGY/

11 LONGITUDINAL STUDY/

12 ((incidence or prevalence or epidemiol$) adj3 (glaucom$ or poag or vision or visual or blind$)).tw.

13 or/8-12

14 7 and 13

15 Middle Aged/

16 elderly.tw.

17 Ethnic and Racial Groups/

18 exp RACE/

19 (race or racial).tw.

20 ethnic$.tw.

21 Familial Incidence/

22 family history.tw.

23 (inherited or familial).tw.

24 MYOPIA/

25 (myopia or myopic).tw.

26 ((short or near) adj2 sight$).tw.

27 (shortsight$ or nearsight$).tw.

28 exp Diabetes Mellitus, Type 2/

29 diabetes.tw.

30 ((exfoliat$ or pseudo-exfoliat$ or pseudo exfoliat$ or pseudoexfoliat$ or pigment$) adj5 (glaucom$ or syndrome or disorder)).tw.

31 pigment$ dispers$ syndrome.tw.

32 central corneal thickness.tw.

33 ((ocular or intraocular or intra-ocular) adj pressure).tw.

34 intraocular pressure abnormality/

35 (cup adj2 disc adj1 ratio).tw.

36 (disc adj1 (haemorrhag$ or hemorrhag$ or bleed$)).tw.

37 or/15-36

38 7 and 37

39 exp RISK/

40 PROGNOSIS/

41 PREDICTION/

42 (risk adj3 (stratif$ or assess$ or factor?)).tw.

43 (risk adj1 relative).tw.

44 (predict$ or prognosis or prognostic).tw.

45 cohort analysis/

46 or/39-45

47 38 and 46

48 14 or 47

Service provision terms

Service provision terms Medline (OVID platform)

1 optometrist$.tw.
2 ophthalmologist$.tw.
3 orthoptist$.tw.
4 Nursing/ or Community Health Nursing/ or Nursing, Team/ or Nursing Staff/ or Nursing Care/ or Nursing Assessment/ or Nursing Staff, Hospital/
5 nurse$.tw.
6 or/1-5

Service provision terms Embase (OVID platform)

1 optometrist$.mp.
2 ophthalmologist$.mp.
3 orthoptist$.mp.
4 nurse$.mp.
5 or/1-4

Service provision terms The Cochrane Library (Wiley Interscience interface)

1 optometrist*
2 ophthalmologist*
3 orthoptist*
4 MeSH descriptor Nursing, this term only
5 MeSH descriptor Community Health Nursing, this term only
6 MeSH descriptor Nursing, Team explode all trees
7 MeSH descriptor Nursing Staff, this term only
8 MeSH descriptor Nursing Care, this term only
9 MeSH descriptor Nursing Assessment, this term only
10 MeSH descriptor Nursing Staff, Hospital, this term only
11 nurse*
12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

Simplified glaucoma/OHT terms

Simplified glaucoma/OHT terms Medline (OVID platform)

1 ocular hypertension/ or exp glaucoma/
2 (ocular hypertension or glaucoma).tw.
3 1 or 2

Simplified glaucoma/OHT terms Embase (OVID platform)

1 Intraocular Hypertension/ or exp glaucoma/
2 (ocular hypertension or glaucoma).tw.
3 1 or 2

Simplified glaucoma/OHT terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Ocular Hypertension explode all trees
2 MeSH descriptor Glaucoma, this term only
3 ocular hypertension
4 glaucoma
5 #1 OR #2 OR #3 OR #4

Surgical/laser intervention terms

Surgical/laser intervention terms Medline (OVID platform)

1 exp Ophthalmologic Surgical Procedures/
2 su.fs.
3 (surgical or surgery).tw.
4 (preoperativ$ or perioperativ$ or postoperativ$).tw.
5 (trabeculectom$ or sclerectom$ or viscocanalostom$ or iridotom$).mp.
6 (cyclo-destruction or cyclodestruction or cyclo-modulation or cyclomodulation).mp.
7 krukenberg spindle$.tw.
8 trabeculoplast$.mp.
9 laser$.mp.
10 or/1-9

Surgical/laser intervention terms Embase (OVID platform)

1 Eye surgery/
2 exp Glaucoma surgery/
3 su.fs.
4 (surgical or surgery).tw.
5 (preoperativ$ or perioperativ$ or postoperativ$).tw.
6 (trabeculectom$ or sclerectom$ or viscocanalostom$ or iridotom$).mp.
7 (cyclo-destruction or cyclodestruction or cyclo-modulation or cyclomodulation).mp.
8 krukenberg spindle$.tw.
9 trabeculoplast$.mp.
10 laser$.mp.
11 or/1-10

Surgical/laser intervention terms The Cochrane Library (Wiley Interscience interface)

1 MeSH descriptor Ophthalmologic Surgical Procedures explode all trees
2 su.fs
3 surgical or surgery
4 preoperativ* or perioperativ or postoperativ*
5 trabeculectom* or sclerectom* or viscocanalostom* or iridotom*
6 cyclo-destruction or cyclodestruction or cyclo-modulation or cyclomodulation
7 krukenberg spindle*
8 trabeculoplast*
9 laser*
10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9

Systematic review filter

Systematic review filter Medline (OVID platform)

1 meta-analysis/
2 (metaanalys$ or meta-analys$ or meta analys$).tw.
3 exp "review literature"/
4 (systematic$ adj3 (review$ or overview$)).tw.
5 (selection criteria or data extraction).ab. and review.pt.
6 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
7 (reference list$ or bibliograph$ or hand search$ or hand-search$ or manual search$ or relevant journals).ab.
8 or/1-7

Systematic review filter Embase (OVID platform)

1 meta analysis/
2 (metaanalys$ or meta-analys$ or meta analys$).tw.
3 systematic review/
4 (systematic$ adj3 (review$ or overview$)).tw.
5 (selection criteria or data extraction).ab. and Review.pt.
6 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or bids or cancerlit).ab.
7 (reference list$ or bibliograph$ or hand search$ or manual search$ or relevant journals).ab.
8 or/1-7

Appendix D

Evidence tables

Evidence Table 1 Diagnostic accuracy of non-contact tonometry vs. Goldmann contact tonometry

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Atkinson et al, 1992[5] **Study design:** Diagnostic **Evidence level:** II	**Patient group:** Patients from general ophthalmology outpatients departments and glaucoma clinics across 3 UK centres. (type of glaucoma not specified) **Exclusion criteria:** Uncooperative patients or those with scarred corneas **All patients** **N:** 403 eyes **Age (median):** NR **M/F:** NR **Drop outs:** NR	**Assessment tool under investigation:** Pulse air non-contact tonometry* measured before Goldmann tonometry. Three different machines: • Machines A and B (same hospital) used at least 3 readings until 3 readings lay within 5mmHg of each other • Machine C (different centre) used 4 successive readings. If any reading >30mmHg a further set was taken with machine set to 30+ mode. **Gold standard:** Goldmann applanation tonometry (GAT) (calibrated Haag-Streit AG Goldmann tonometer. • Measured within 3 minutes of pulse air reading. Patients did not move from position between measurement and instillation of oxybuprocaine 0.4% & fluorescein.	**Machine A (64 eyes) †** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test odds Post-Test Odds (Probability) +ve result Post-Test Probability -ve result **Machine B (223 eyes) †** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test odds Post-Test Odds (Probability) +ve result Post-Test Probability -ve result **Machine C (116 eyes) †** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test odds Post-Test Odds (Probability) +ve result Post-Test Probability -ve result	 81% 93% 85% 93% 31% 12.47 0.16 0.45 5.67 (85%) 5.28 (84%) 40% 95% 84% 71% 40% 8.1 0.63 0.65 5.29 (84%) 1.34 (57%) 48% 94% 63% 89% 18% 7.54 0.56 0.22 1.67 (63%) 1.12 (53%)	**Funding:** Not reported **Limitations:** Number of eyes were recruited was reported but not the number of patients. Does not report the proportion of patients with glaucoma or ocular hypertension. **Also reported:** mean (SD) IOP , and correlation coefficient (r) and linear regression equation (between two; mean (SD) differences in IOP between type of tonometer; **Additional Notes:** † (ability to detect a Goldmann IOP >21mmHg) Observer masked * Study presented as 3 studies, 3 machines used in two centres

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, Sig=statistically significant at 5%, N=total number of patients randomised, CI95%= 95% Confidence Interval

Evidence Table 2 Diagnostic accuracy of non-gonioscopic methods vs. gonioscopy

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Baskaran et al., 2007[9] **Study design:** Diagnostic **Evidence level:** III	**Patient group:** Phakic subjects with narrow angles and normal subjects with closed angles attending glaucoma or general ophthalmology clinics in the Singapore National Eye Centre. **Exclusion criteria:** Subjects with corneal disorders and uveitis excluded **<u>All patients</u>** **N:** 120 (120 eyes) **Age (mean ± SD):** 62.1 ± 11.3 **M/F:** 52/68 73% Chinese 7% Malay 20% Indian **Drop outs:** 0 **Diagnosis:** 44% PACG 56% POAG	**Reference standard:** Gonioscopy: static and indentation with 2 or 4 mirror prisms. For gonioscopy: narrow angle defined as the presence of a Schaffer grade of up to 1 (10° iridotrabecular angle) for at least 180° of the angle on gonioscopy with or without peripheral anterior synchae **Assessment tool under investigation:** Scanning peripheral Anterior Chamber Depth analyzer (SPAC) and modified Van Herick's grade Van Herick's test. Peripheral anterior chamber depth of ≤25% of the corneal thickness as angle closed and ≥40% angle open as optimal cut-off using standard photos For SPAC: 3 categorical grades for risk of angle closure S=suspect ≥4 points exceeding 95% CI; P=potential ≥4 points exceeding 72% CI; N=normal. Optimal cut-off is S or P as closed and N as open angle	**Detection of angle-closure by eye using Van Herick's test at cut off ≤25%** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result	 85% (45/53) 90% (60/67) 87% (45/52) 88% (60/68) 44% (53/120) 8.13 0.17 0.44 87% (CI95% 76 – 93%) 12% (CI95% 7 – 20%)	**Funding:** National Medical research Council, Singapore **Limitations:** Asian population (73% Chinese) where PACG is more prevalent. It was not clear whether Van Herick's test was performed independently and in a masked fashion to gonioscopy. **Additional Outcomes:** **Notes:** SPAC assessment observer was masked to results of gonioscopy and Van Herick's test
			Detection of angle-closure by eye using Van Herick's test at cut off ≤5% to ≥15%	Sensitivity 30% (16/53) Specificity 100% (67/67)	
			Detection of angle-closure by eye using Van Herick's test at cut off ≤15% to ≥25%	Sensitivity 60% (32/53) Specificity 100% (67/67)	
			Detection of angle-closure by eye using Van Herick's test at cut off ≤40% to ≥75%	Sensitivity 96% (51/53) Specificity 76% (51/67)	
			Detection of angle-closure by eye using SPAC at cut off S,P =closed angle (N=open) Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result	 85% (45/53) 73% (49/67) 71% (45/63) 868% (49/57) 44% (53/120) 3.16 0.21 0.44 71% (CI95% 62 – 79%) 14% (CI95% 8 – 24%)	

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
			Detection of angle-closure by eye using SPAC at cut off S =closed angle (P, N=open)	Sensitivity 60% (32/53) Specificity 85% (57/67)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, Sig=statistically significant at 5%, N=total number of patients randomised, CI95%= 95% Confidence Interval

Non-gonioscopic methods vs. gonioscopy (continued)

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Nolan et al., 2007[112] **Study design:** Diagnostic test **Evidence level:** II	**Patient group:** Patients with suspected or confirmed primary angle closure (PACG). Patients with POAG, OHT and cataracts were also included. All patients were from glaucoma clinics at the University Hospital of Singapore. **Inclusion criteria:** ≥40 years **Exclusion criteria:** Patients with pseudophakia or previous glaucoma surgery **<u>All patients</u>** **N:** 203 (342 eyes) **Age (median):** 62.5 (range, 40-86) **M/F:** 80/123 **Drop outs:** 3* **Diagnosis:** 17% Normal 33% Suspected/confirmed narrow angles 37% PACG 7% POAG 6% Other	**Reference standard:** Gonioscopy using Goldmann 2 mirror lens & Sussmann 4-mirror lens. Angle closure defined by gonioscopy as a Spaeth grade of 0° ≥1 Quadrant (posterior trabecular meshwork not visible) **Assessment tool under investigation:** Non-contact anterior segment optical coherence tomography (AS-OCT) (Carl Zeiss Meditec) **AS-OCT**: angle closure defined by as contact between the peripheral iris and angle wall anterior to scleral spur. Individuals classified as angle closure if ≥1 quadrants of the angle closed in either eye	**Detection of angle-closure by individual (one or both eyes)** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result **Detection of angle-closure by eye** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result	 98% (97/99) 55% (56/101) 68% (97/142) 97% (56/58) 50% (99/200) 2.20 0.04 0.50 68% (CI95%: 63 – 73%) 4% (CI95%: 1 – 13%) 94% (143/152) 55% (105/190) 63% (143/228) 92% (105/114) 44% (152/342) 2.10 0.11 0.44 63% (CI95%: 59 – 66%) 8% (CI95%: 5 – 14%)	**Funding:** National University of Singapore **Limitations:** Patients in Asian population where PACG is more prevalent. **Additional Outcomes:** **Notes:** *In 3 subjects it was not possible to obtain gonioscopic readings or OCT images Investigators were masked to gonioscopy results

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, Sig=statistically significant at 5%, N=total number of patients randomised, CI95%= 95% Confidence Interval

Non-gonioscopic methods vs. gonioscopy (continued)

Study details	Patients	Diagnostic tools	Measure of Disorders	Results	Comments
Thomas 1996[149] **Study design:** Diagnostic test **Evidence level:** II	**Patient group:** New patients attending outpatient clinic Christian Medical College, Vellore, India (type of glaucoma not specified) **Exclusion criteria:** Patients with acute conditions (4 patients were excluded: phacolytic glaucoma, phacomorphic glaucoma and corneal ulcer) **<u>All patients</u>** **N:** 96 (96 eyes) **Age (mean):** 45.45 (range 14 to 74, SD 14.90) **M/F:** 50/46 **Drop outs:** 4	**Assessment tool under investigation:** Flashlight test (1/2 and 1/3 shadow) Van Herick's test **Reference standard:** Gonioscopy performed on Haag Streit slit lamp and Goldmann single mirror goniolens followed by Sussmann 4-mirror lens for examination of peripheral anterior synchae suggestive of angle closure by glaucoma specialist. **Flashlight** – crescentic shadow formed from beam directed parallel to the iris was graded according to area between the limbus and pupillary edge. 4 grades used: more than ½ ; ½ to 1/3; minimal and no shadow **Van Herick's test** If peripheral anterior chamber depth (PACD) was ≥ to corneal thickness recorded as grade 4; 50% corneal thickness = grade 3; 25% corneal thickness = grade 2 and < 25% corneal thickness = grade 1. ***Grade 1 taken as narrow***	**Flashlight test (1/2 iris shadow)** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result **Flashlight test (1/3 iris shadow)** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result **Van Herick's test (cut off = grade 1)** Sensitivity Specificity Positive predictive value Negative predictive value Prevalence Positive Likelihood Ratio Negative Likelihood Ratio Pre-test Probability (CI 95%) Post-Test Probability +ve result Post-Test Probability -ve result	 48% (10/21) 83% (62/75) 43% (10/23) 85% (62/73) 22% (21/96) 2.75 0.63 0.22 44% (CI95%: 28 – 60%) 15% (CI95%: 11 – 21%) 86% (18/21) 71% (53/75) 45% (18/40) 95% (53/56) 22% (21/96) 2.92 0.2 0.22 45% (CI95%: 36 – 55%) 5% (CI95%: 2 – 14%) 62% (13/21) 89% (67/75) 62% (13/21) 89% (67/75) 22% (21/96) 5.80 0.43 0.22 62% (CI95%: 44 – 77%) 11% (CI95%: 7 – 17%)	**Funding:** NR **Limitations:** Patients in Indian population where PACG is more prevalent. **Additional Outcomes:** Flashlight Test (one third shadow) OR Van Herick's Test Flashlight Test (one third shadow) AND Van Herick's Test Gonioscopy grading (Goldman single mirror) **Notes:** Diagnostic parameters were recalculated for figures estimated for 2x2 tables using the prevalence 21/96 and reported figures for sensitivity and specificity Gonioscopy was carried out immediately after the other diagnostic test under investigation One eye selected randomly from each patient Glaucoma specialist was masked to the previous test results

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, Sig=statistically significant at 5%, N=total number of patients randomised, CI95%= 95% Confidence Interval

Evidence Table 3 Any treatment vs. no treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kass et al., 2002[72] Ocular Hypertension Treatment Study (OHTS) **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** Median follow-up for African American participants 72 months and 78 months for other participants.	**Patient group:** OHT patients **Inclusion criteria:** Age between 40-80 years, a qualifying IOP between 24 mmHg and 32 mmHg in one eye and between 21 mmHg and 32 mmHg in the other eye, gonioscopically open angles, 2 normal and reliable visual field tests per eye and normal optic discs **Exclusion criteria:** Visual acuity worse than 20/40 in either eye, previous intraocular surgery (other than uncomplicated cataract extraction with posterior chamber lens implantation), and diabetic retinopathy or other diseases capable of causing visual field loss or optic disc deterioration. **Setting**: 22 clinical centres, USA **<u>All patients</u>** **N:** 1636 **<u>Group 1</u>** **N:** 817 **N medication withdrawn**:40 **M/F:** 359/458 **Age categories:** 40 to ≤ 50 years: 291 (35.6%) >50 to ≤ 60 years: 270 (33.0%) >60 to ≤ 70 years: 202 (24.7%) >70 to 80 years: 64 (6.6%) **Previous use of OHT medication**: 35.0% **First-degree family history of glaucoma**: 34.0%	**Group 1** Topical ocular hypotensive medication. Treatment to achieve a target IOP of 24 mm Hg or less and a minimum 20% reduction in IOP from the average of the qualifying IOP and IOP at the baseline randomisation visit. Topical medication was changed and/or added until both of these goals were met or the participant was receiving maximum tolerated topical medical therapy. Medications were added and changed in one-eyed therapeutic trials. Included all topical ocular hypotensive medications commercially available in the US. Follow-up visits every six months. **Group 2** No treatment	**Patients developed POAG** (end points of visual field abnormality or optic disc deterioration)	**Group1:** 36/817 (4.4%) African American: 14/203 Other: 22/614 **Group 2:** 89/819 (10.9%) African American: 26/205 Other: 63/614	**Funding:** Study was supported by grants EY09341 and EY09307 from the National Eye Institute and the National Centre on Minority Health and Health Disparities, National Institutes of Health, Bethesda, Md; Merck Research Laboratories, White House Station, NJ; and by an unrestricted grant from Research to Prevent Blindness, New York, NY. **Limitations:** Patient and clinician were not blinded to randomisation during follow-up. **Additional outcomes:** Cumulative probability of developing a reproducible visual field abnormality or an optic disc deteriorations due to POAG or a variety of other caused was reported. Estimated of the effect of treatment after adjusting.
			Cumulative probability of developing POAG	**Hazard Ratio:** 0.40 (95% CI: 0.27 to 0.59) **p value:** <0.0001	
			Cumulative probability of developing POAG at 60 months:	**Group1:** 4.4% **Group 2:** 9.5%	
			Cumulative probability of developing POAG	**African-American participants:** Hazard ratio: 0.54 (95% CI:0.28-1.03 **Other participants:** Hazard ratio: 0.34 (95% CI:0.21-0.56 P=0.26	
			Change in IOP	**Group 1:** Baseline: 24.9±2.6 Reduction from baseline: -22.4%±9.9 **Group 2:** Baseline: 24.9±2.7 Reduction from baseline: -4.0%±11.6	
			Adverse effects:	**Ocular symptoms:** **Group1:** 57% **Group 2:** 47% **P value:** <0.001 **Symptoms affecting skin, hair or**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Myopia ≥1-diopter spherical equivalent: 34.4% **Oral B-adrenergic antagonist:** 5.4% **Oral calcium channel blocker:** 12.8% **History of migraine:** 10.4% **History of diabetes:** 11.5% **History of hypertension:** 37.5% **History of low blood pressure:** 4.8% **History of cardiovascular disease:** 6.8% **History of stroke:**0.9% **Drop outs:** 115 (28 died) **<u>Group 2</u>** **N:** 819 **N medication initiated:**42 **M/F:** 346/473 **Age categories:** 40 to ≤ 50 years: 287 (35.0%) >50 to ≤ 60 years: 259 (31.6%) >60 to ≤ 70 years: 210 (25.6%) >70 to 80 years: 63 (7.7%) **Previous use of OHT medication:** 39.3% **First-degree family history of glaucoma:** 35.6% **Myopia ≥1-diopter spherical equivalent:** 33.7% **Oral B-adrenergic antagonist:** 4.6% **Oral calcium channel blocker:** 14.0% **History of migraine:** 11.7% **History of diabetes:** 12.1% **History of hypertension:** 38.1% **History of low blood pressure:** 4.0% **History of cardiovascular disease:** 6.5% **History of stroke:** 1.6% **Drop outs:** 113 (29 died)			**nails:** **Group1:** 23% **Group 2:** 18% **P value:** <0.001	Treatment benefit for reproducible visual field abnormality attributed to POAG and for reproducible optic disc deterioration attributed to POAG reported. **Notes:** Randomisation method was adequate and primary outcome assessment was masked. 3328 screened but 1636 entered into study (1692 not eligible for various reasons).
			Difference between groups total hospitalisations	**P=0.56**	
			Difference between groups worsening of pre-existing conditions	**P=0.28**	
			Difference between groups mortality rates	**P=0.70**	
			Other adverse events (≥10%) **Tearing/watering** **Itching** **Blurry or dim vision** **Feels like object in eye** **Poor night vision** **Difficulty Sleeping** **Headache** **Loss of libido** **Numbness/tingling arms**	**Medication (%)** **(%)** **12.6** **11.4** **11.4** **10.1** **12.2** **17.2** **10.7** **11.2** **13.9** **Observation** **13.2** **11.8** **11.6** **10.6** **11.8** **16.8** **11.8** **12.6** **16.3**	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Any treatment vs. no treatment (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Heijl et al., 2002[59] Early Manifest Glaucoma Trial (EMGT) **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** At least 6 years. Open label design but outcome measurement was masked	**Patient group:** patients with chronic open angle glaucoma **Inclusion criteria:** Men and women with newly diagnosed, previously untreated COAG (POAG, NTG or PEX) with repeatable visual field defects in at least one eye measured using Humphrey 24-2 full programme. Age between 50 and 80 years **Exclusion criteria:** • Advanced visual field defects (MD-16dB or threat to fixation) • Visual acuity < 0.5 • Mean IOP >30 mmHg • Lens opacities exceeding N1, C1 or P1 in Lens Opacities Classification System • Patients with glaucomatous visual field defects in both eyes eligible if MD = -10 dB or better in one eye and -16 dB in other eye. **Setting:** 2 clinical centres (1 reading and 1 co-ordinating), Sweden **<u>All patients</u>** **N:** 255 **<u>Group 1</u>** **N:** 129 **Both eyes eligible:**: 34 (26%) **One eye eligible:** 95 (74%) **Age ± SD:** 68.2 ± 4.8 (range 58-78) **M/F:** 47/82 **Mean Baseline IOP mmHg ± SD:** 20.6 ± 4.1 **Patients with IOP < 21 mmHg:** 69 **Mean Visual Acuity:** ± SD: 0.9 ± 0.1	**Group 1** Betaxolol 5 mg/ml 2/day and argon laser trabeculoplasty (ALT) 360 degrees performed 1 week after inclusion. If eligible eye achieved 25 mmHg in 2 consecutive visits or other eye was 35 mmHg in 1 visit then latanoprost 50 µm/day. **Group 2** No treatment **Examination methods:** Patients were followed up at 3 month intervals for visual acuity, Goldmann tonometry, Humphrey 30-2 Full threshold visual field testing, ophthalmoscopy, slit lamp examination and optic disc photographs every 6 months. *Visual field progression defined as worsening of 3 consecutive points in the Glaucoma Change Probability map, confirmed by 3 consecutive visual fields.	**Glaucoma progression (visual or optic disc changed*) after follow up of 48 months** Data from Rolim et al., 2007[124]	**Group 1:** 39/129 (30%) **Group 2:** 62/126 (49%) **p value:** 0.002 (calculated by NCC-AC Chi-squared test)	**Funding:** Study was supported by grants U10EY10260 and U10EY10261 from the National Eye Institute, Bethseda, USA and K2002-74X-10426-10A from the Swedish Research Council, Stockholm **Limitations:** **Additional outcomes:** Health-related quality of life scores **Notes:** Randomised using computer generated sequence. Computerised visual field and optic disc photographs read by masked observers. IOP evaluation also masked. An Intention to Treat analysis was used. Patients and clinicians were not masked to treatment allocation
			Glaucoma progression (visual field and optic disc) after 6 years (range 51-102 months	**Group 1:** 58/129 (45%) **Group 2:** 78/126 (62%) **p value:** 0.07	
			Visual field progression alone after 6 years (range 51-102 months	**Group 1:** 57/129 (44%) **Group 2:** 78/126 (62%) **p value:** 0.005 (calculated by NCC-AC Chi-squared test)	
			Ocular side effects (reduction in visual acuity, floaters or conjunctivitis)	**Group 1:** 21/129 (16%) **Group 2:** 16/126 (13%) **p value:** 0.43 (calculated by NCC-AC Chi-squared test)	
			Systemic side effects (asthma, bradycardia, depression)	**Group 1:** 6/129 (4.6%) **Group 2:** 1/126 (0.8%) **p value:** 0.12 (calculated by NCC-AC Fishers exact test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Mean deviation ± SD: -5.0 ± 3.7 dB **Number of optic disc abnormalities (cupping, notching, haemorrhage):** 147 **Myopia ≤1-diopter spherical equivalent**: 19(12%) **Exfoliation Syndrome**: 9 (6%) Disease History: **Family history of glaucoma**: 26 (20%) 34.4% **Cardiovascular disease**: 19 (15%) **Stoke/low blood pressure**: 12 (9%) **General artheriosclerosis**: 4 (3%) **Peripheral vasospasms and migraine**: 21 (16%) **Pulmonary disease**: 3 (2%) **Diabetes**: 3 (2%) Medication use: **Antihypertensives**: 31 (24%) **Corticosteroids**: 0 **Insulin or oestrogen**: 57 (44%) **Drop outs:** 24 (3 lost to follow up, 15 died, 6 received ALT but discontinued medications) **<u>Group 2</u>** **N:** 126 **Both eyes eligible**: 27 (21%) **One eye eligible**: 99 (79%) **Age ± SD:** 68.0 ± 5.0 (range 50-79) **M/F:** 39/87 **Mean Baseline IOP mmHg ± SD**: 20.9 ± 4.1 **Patients with IOP < 21 mmHg**: 63 **Mean Visual Acuity**: ± SD: 1.0 ± 0.1 **Mean deviation ± SD**: -4.4 ± 3.3 dB **Number of optic disc abnormalities (cupping, notching, haemorrhage):** 138 **Myopia ≤1-diopter spherical equivalent**: 23(15%) **Exfoliation Syndrome**: 16 (10%) Disease History: **Family history of glaucoma**: 24 (19%)	*Optic disc progression detected from baseline line and follow up photographs by a masked reader using flicker chronoscopy and			

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	34.4% **Cardiovascular disease:** 14 (11%) **Stoke/low blood pressure:** 5 (4%) **General artheriosclerosis:** 5 (4%) **Peripheral vasospasms and migraine:** 26 (21%) **Pulmonary disease:** 0 **Diabetes:** 6 (5%) Medication use: **Antihypertensives:** 31 (25%) **Corticosteroids:** 4 (3%) **Insulin or oestrogen:** 55 (44%) **Drop outs:** 10 (3 lost to follow up, 7 died)				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Any treatment vs. no treatment (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Collaborative Normal-Tension Glaucoma Study Group, 1998[24] Collaborative Normal-Tension Glaucoma Study (CNTGS) **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 5 years.	**Patient Group:** Normal tension glaucoma **Inclusion criteria:** Unilateral or bilateral normal tension glaucoma with optic disc abnormalities and visual field defects and IOP ≤ 24 mmHg in either eye. Age 20 to 90 years. After 4 week washout patients required to have a median of 10 IOP readings of ≤ 20 mmHg and 3 good baseline visual fields. **Exclusion criteria:** • Patients on systemic beta-blockers or clonidine. • Patients unable to perform visual field test • Eyes with previous laser treatment, ocular surgery • Eyes with traumatic VF defects • Narrow angles • Best correct visual acuity of < 20/30 • Baseline visual fields too damaged to record further progression **Setting**: 24 clinical centres, international **<u>All patients</u>** **N:** 145 **<u>Group 1</u>** **N:** 79 **Age ± SD:** 65.5 ± 9.6 **M/F:** 30/49 **Mean IOP at randomisation mmHg ± SD**: 16.1 ± 2.3	**Group 1** Achieved 30% change in IOP using medical or surgical interventions except for beta-blockers or adrenergic agonists. **Group 2** No treatment **Examination methods:** Patients were followed up at 3 month intervals for first year and every 6 months thereafter. Tests performed for visual acuity, visual field using Humphrey and appearance of optic disc and optic disc photographs every year. Visual field progression was defined by deepening of existing scotoma, expansion of an existing scotoma or new or expanded threat to fixation (cluster of 3 points) or fresh scotoma in previously normal part of visual field. *Visual field progression was confirmed by 4/5 consecutive follow up visits showed progression relative to baseline.	**Glaucoma progression (optic disc or visual field progression*)** Data from Sycha et al., 2003[146]	**Group 1**: 22/61 (31%) **Group 2**: 31/79 (39%) **p value**: 0.7 (calculated by NCC-AC Chi-squared test)	**Funding:** Glaucoma research Foundation with grants from Oxnard Foundation and Edward J Daly Foundation, San Francisco, USA **Limitations:** Allocation concealment and masking of outcome assessment was not clearly reported **Additional outcomes:** **Notes:** Randomisation using block randomisation scheme occurred after selected eye had a visual field defect that threatened fixation. Intention to treat analysis was performed The study was carried out before the introduction of topical carbonic anhydrase inhibitors and prostaglandin analogues.
			Visual Field Progression*	**Group 1**: 11/61 (18%) **Group 2**: 24/79 (30%) **p value**: 0.09 (calculated by NCC-AC Chi-squared test)	
			Cataract Formation	**Group 1**: 23/61 (38%) **Group 2**: 11/79 (14%) **p value**: 0.011 (calculated by NCC-AC Chi-squared test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Visual Acuity: 0.89 ± 2.86 **Mean deviation at randomisation ± SD:** -7.54 ± 4.31 dB **Refraction:** -0.66 ± 2.86 Ethnicity **Asian:** 9 **Black:** 2 **Hispanic:** 2 **White:** 65 **Drop outs:** 5 **Group 2** **N:** 61 **Age ± SD:** 66.3 ± 10.3 **M/F:** 17/44 **Mean IOP at randomisation mmHg ± SD:** 16.9 ± 2.1 **Visual Acuity:** 0.89 ± 0.15 **Mean deviation at randomisation ± SD:** -8.38 ± 5.26 dB **Refraction:** -1.09 ± 3.3 Ethnicity **Asian:** 3 **Black:** 5 **Hispanic:** 1 **White:** 51 **Drop outs:**	Optic disc damage was independently assesses by masked observers using stereo photographs and agreed.			

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 4 Beta-blockers vs. no treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Vass et al., 2007[155] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum treatment 12 months (range 12 months to 10 years).	**Patient group:** All people with Ocular Hypertension (POAG patients included but all the studies in this category were in OHT patients). **Inclusion criteria:** Minimum treatment duration 1 year. People with a mean IOP above 21 mm Hg. **Exclusion criteria:** Patients with Normal Tension Glaucoma. Trials excluded on methodology if graded inadequate on allocation concealment. **<u>All patients</u>** **N:** 4979 from 26 trials **Age (mean):** NR **M/F:** NR **Drop outs:** NR Caucasian: 2907 African: 562 Hispanic: 59 Asian: 15 Race NR: 16 trials Sample range: 18-1636	**Group 1** Beta-blocker **Group 2** Placebo or no treatment.	**Incidence of visual field defect progression: (OHT patients)** **Sensitivity analysis** **Drop outs due to drug related adverse events:** **Long-term studies concerning incidence of visual field progression (follow-up of at least 3 years):**	**Group1 (beta-blocker):** 45/469 (9.6%) **Group 2 (placebo/untreated):** 64/466 (13.7%) **Peto OR:** 0.67 (95% CI: 0.45, 1.00); 8 studies Heterogeneity: Chi^2=4.00, df=6 (P=0.68), I^2=0% **Group 1:** 18/253 **Group 2:** 26/246 **OR:** 0.64 (95% CI: 0.34, 1.19); 4studies Heterogeneity: Chi^2=0.17, df=2 (P=0.92), I^2=0% **Group1:** 17/255 **Group 2:** 14/248 **Peto OR:** 1.24 (95% CI: 0.59, 2.58); 4 studies Heterogeneity: Chi^2=2.05, df=2 (P=0.36), I^2=2.4% **Group1:** 44/444 **Group 2:** 62/438 **Peto OR:** 0.67 (95% CI: 0.45, 1.01); 6 studies Heterogeneity: Chi^2=3.91, df=5 (P=0.56), I^2=0%	**Funding:** Department of Ophthalmology and Clinical Pharmacology, University of Vienna **Limitations:** IOP change from baseline not reported as an outcome Quality assessment not reported in detail for each trial **Additional outcomes:** Interclass comparisons. Sensitivity analysis also conducted to determine the effect of excluding trials falling below a quality threshold with either exclusion of trials scoring C (inadequate) on any aspect of methodological trial quality or exclusion of trials which had assumed that eyes within an individual were independent (fellow eye used as a control group). **Notes:** Studies included in Vass 2007 that do not meet guideline inclusion criteria because eyes were randomised Wishart & Batterbury, 1992 and Kass et al., 1989

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

RCTs included in VASS 2007 that meet guideline inclusion criteria

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Quality Check	Notes
Epstein et al., 1989[42] [USA]	Timolol 0.5% 2/day v No treatment	5 years	Glaucoma Clinical Centre & MSD	OHT	107	60	BB: 24.0 ± 1.3 NT: 23.9 ± 1.6	10 / 62	Randomisation Method: NR Allocation concealment: N Masked outcome assessment: Y Incomplete outcome data: N ***Moderate risk of bias***	No IOP figures, estimate from graph. **Open label** No previous treatment. VF defects using Goldmann or Octopus perimeters
Heijl & Bengtsson, 2000[58] [Sweden]	Timolol 0.5% 2/day v Placebo	10 years	MSD, Järnhardt Foundation & Malmö Hospital	OHT (30% PEX or PG)	90	63	BB: 27.1 ± NR NT: 26.2 ± NR	NR / 38	Randomisation method: Y Allocation concealment: Y Masked outcome assessment: Y Incomplete outcome data: N ***Low risk of bias***	Eyes with previous antiglaucoma therapy were permitted with a wash-out of 2 weeks.
Kamal et al., 2003[69] [UK]	Betaxolol 0.5% 2/day v Placebo	5 years	Guide Dogs for the Blind, Blue Light Fund & Alcon	OHT	356	66 (>35)	BB: 26.3 ± 2.3 NT: 25.6 ± 2.2	NR / NR	Randomisation method: Y Allocation concealment: Y Masked outcome assessment: Y Incomplete outcome data: N ***Low risk of bias***	No previous treatment. Conversion to glaucoma defined by AGIS criteria
Kitazwa, 1990[76] [Japan]	Timolol 0.5% 2/day v Placebo	2 years	NR	OHT	20	NR	NR	NR / NR	Randomisation method: NR Allocation concealment: NR Masked outcome assessment: NR Incomplete outcome data: N ***High risk of bias***	No IOP data. Study does not report whether treatment was 1st option VF defects using Humphrey perimeter
Schulzer et al., 1991[131] [Canada]	Timolol 0.25% - 0.5% 2/day v No Treatment	6 years	MSD & Canadian MRC	OHT	137	60 (>45)	BB: 26.3 ± 3.5 NT: 26.1 ± 3.2	NR / 31	Randomisation method: NR Allocation concealment: NR Masked outcome assessment: Y Incomplete outcome data: N ***Moderate risk of bias***	**Open label** No previous treatment. VF defects using Goldmann or Octopus perimeters

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Quality Check	Notes
Schwartz et al., 1995[134] [USA]	Timolol 0.5% 2/day v Placebo	1 to 2 years	MSD	OHT (43% PEX or PG)	37	60	BB: 23.1 ± 2.5 NT: 23.7 ± 3.6	8 / 22	Randomisation method: Y Allocation concealment: NR Masked outcome assessment: Y Incomplete outcome data: N ***Low risk of bias***	Results by presented by eye No previous treatment. VF defects using Goldmann perimeter

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 5 Timolol 0.5% vs. timolol 0.25%

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Mills1983[101] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** patients with chronic open angle glaucoma **Setting:** Manchester, UK **Inclusion criteria** Patients with optic nerve head and visual field changes of open angle glaucoma, either controlled on topical glaucoma medication or presenting as new patients. **Exclusion criteria:** Patients with a history of cardiovascular disease or bronchospasm or who were receiving concomitant medication for a cardiovascular disease. **<u>All patients</u>** **N:** 30 **Age (mean ± SD):** 70 ± 8.8 **M/F:** 16/14 **Mean IOP:** NR **Drop outs:** 9 **<u>Group 1</u>** **N:** 15 **Age (mean):** 71 **M/F:** 9/6 **Mean IOP:** 26.9 ± 5.1 (RE), 26.8 ± 5.5 (LE) **Drop outs:** 4 in total. 3 required additional treatment as pressure not adequately controlled by Timolol alone) and 1 had elevated IOP immediately after instillation of treatment which was therefore discontinued) **<u>Group 2</u>**	**Group 1** Timolol 0.25% twice daily **Group 2** Timolol 0.5% twice daily **All** 7 day wash-out period for patients on topical glaucoma therapy Each patient had a day curve of IOP at 0900, 1200, 1600 and 2000) measured by Goldmann applanation tonometry and Haag-Streit slit lamp. A mean of the day curve pressures was calculated. Patients were reviewed at 1, 3, 6, 9 and 12 months.	**Mean ± SD diurnal IOP at baseline (mm Hg)**	**Group 1:** 26.9± 5.1(RE), 26.8± 5.5 (LE) **Group 2:** 24.2 ± 3.75 (RE), 25.4 ± 4.1 (LE) **95% CI:** NR **p value:** NR	**Funding:** NR **Limitations:** 8 patients (3 group 1 and 5 group 2) required further treatment to control their IOP and were given pilocarpine. These patients weren't included in the final analysis. **Additional outcomes:** Side effects were few. 1 patient complained of occasional hallucinations and 2 of tinnitus which was temporary **Notes:**
			Mean ± SD diurnal IOP at 6 months (mm Hg)	**Group 1:** 20.5 ± 4.3 (RE), 20.1 ± 3.2 (LE) **Group 2:** 20.1 ± 4.2 (RE), 21.2 ± 3.9 (LE) **95% CI:** NR **p value:** 0.8 (RE); 0.4 (LE)	
			Mean ± SD diurnal change in IOP from baseline at 6 months (mm Hg)	**Group1:** 6.4 ± 4.3 (RE), 6.7 ± 3.2 (LE) **Group 2:** 4.1 ± 4.2 (RE), 4.2 ±3.9 (LE) **95% CI:** NR **p value:** 0.14 (RE); 0.04 (LE)	
			Mean ± SD diurnal IOP at 9 months (mm Hg)	**Group 1:** 18.4 ± 4.4 (RE), 18.6 ± 2.9 (LE) **Group 2:** 17.5 ± 3.8 (RE), 19.1± 4.3 (LE) **95% CI:** NR **p value:** 0.55 (RE); 0.71 (LE)	
			Mean ± SD diurnal change in IOP from baseline at 9 months (mm Hg)	**Group1:** 8.5 ± 4.4(RE), 8.2 ± 2.9(LE) **Group 2:** 6.7 ± 3.8 (RE), 6.3 ±4.3 (LE) **95% CI:** NR **p value:** 0.22 (RE); 0.16 (LE)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 15 **Age (mean):** 69 **M/F:** 6/9 **Mean IOP:** 24.2 ± 3.75 (RE), 25.4 ± 4.1 (LE) **Drop outs:** 5 (additional treatment was needed as pressure not adequately controlled by Timolol alone)		**Mean ± SD diurnal IOP at 12 months (mm Hg)**	**Group 1:** 20.0 ± 2.5 (RE), 20.8 ± 2.1 (LE) **Group 2:** 19.4 ± 2.3 (RE), 20.2 ± 3.6 (LE) **95% CI:** NR **p value:** 0.49 (RE); 0.58 (LE)	
			Mean ± SD diurnal change in IOP from baseline at 12 months (mm Hg)	**Group1:** 6.9 ± 2.5 (RE), 6.0 ± 2.1 (LE) **Group 2:** 4.8 ± 2.3 (RE), 5.1 ± 3.6 (LE) **95% CI:** NR **p value:** 0.02 (RE); 0.40 (LE)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 6 Prostaglandin analogues vs. beta-blockers

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Alm & Stjernschantz, 1995[4] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG & OHT **Setting:** multi-centre across 13 Scandinavian eye clinics **Inclusion criteria:** • Age ≥ 40 years old • Unilateral or bilateral POAG or pigmentary glaucoma or exfoliation glaucoma or OHT ≥ 22 mmHg. • Completion of adequate washout period for sympathomimetics, CAI and miotics. **Exclusion criteria:** • Patients on topical beta blockers within 6 months of study • Angle closure glaucoma history • Ocular trauma • Previous filtration or laser surgery for glaucoma within 6 months of study • Dry eye syndrome • Ocular inflammation or infection within 3 months of study • Contact lens wearers • Those with contraindications for beta blockers • Patients who would not benefit from monotherapy	**Group 1** Latanoprost 0.005% in morning followed by placebo in evening for first 3 months then regimen reversed for next 3 months **Group 2** Latanoprost 0.005% in evening preceded by placebo in morning for first 3 months then regimen reversed for next 3 months **Group 3** Timolol 0.5% 2/day for 6 months **Examination methods:** IOP measured by Goldmann Applanation Tonometry - 3 readings taken in each eye (8 am, 12 noon and 4 pm) and mean used for statistical analysis. (Average of 2 eyes used for bilateral patients) Visual acuity readings, slit lamp examination and blood and urine samples taken throughout study. Photographs of iris taken and classified by independent evaluator Visual fields examined using	**Mean ± SD* baseline diurnal IOP mmHg**	**Group1:** 24.8 ± 3.77 **Group 2:** 25.5 ± 2.91 **Group 3:** 24.6 ± 2.75	**Funding:** Supported by Pharmacia (now Pfizer), Sweden which manufactures latanoprost. **Limitations:** Allocation concealment was not reported. Not known if the statistical calculations are done on an ITT basis. Number of patients remaining at the end of the study does not add up to figures in table listing reasons for withdrawal **Additional outcomes:** Detailed analysis of conjunctival hyperaemia **Notes:** *SD = SE*√n **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from
			Mean ± SD* end point diurnal IOP (6 mths) mmHg	**Group1:** 16.2 ± 2.83 **Group 2:** 17.7 ± 2.91 **Group 3:** 17.9 ± 2.75	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)	**Group1:** 8.6 ± 4.06** **Group 2:** 7.8 ± 3.51** **Group 3:** 6.7 ± 2.99**	
			Change in IOP in Group 1 versus Group 3 at 6 mths	**Group1:** 8.6 ± 4.06** **Group 3:** 6.7 ± 2.99** **p value:** <0.001 (using ANCOVA)	
			% patients at 6 mths reaching acceptable IOP ≤ 17 mmHg	**Group1:** 58/84 (69%) **Group 2:** 27/79 (34%) **p value:** <0.001 (Chi-squared test)	
			Apparent deterioration or visual field	**Groups 1 + 2:** 0 **Group 3:** 1	
			Disc Haemorrhage	**Groups 1 + 2:** 3 **Group 3:** 3	
			Total number of local ocular side effects by group	**Groups 1 + 2:** 86 **Group 3:** 41 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation	**Groups 1 + 2:** 7 **Group 3:** 0	
			Total number of cardiovascular systemic side effects by group	**Groups 1 + 2:** 20 **Group 3:** 18 Includes upper respiratory tract infection, angina, thrombophlebitis	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	<u>All patients</u> **N:** 267 **Age (mean):** 67 (40-85) **M/F:** 116/151 **Drop outs:** 15 **Race**: NR **<u>Group 1</u>** **N:** 89 **Age (mean):** 67 (40-84) **M/F:** 39/50 **Drop outs:** 5 **OHT:** 43 **COAG:** 46 **<u>Group 2</u>** **N:** 94 **Age (mean):** 67 (44-85) **M/F:** 43/51 **Drop outs:** 9 **OHT:** 44 **COAG:** 50 **<u>Group 3</u>** **N:** 84 **Age (mean):** 66 (42-84) **M/F:** 34/50 **Drop outs:** 5 **OHT:** 36 **COAG:** 48	Humphrey 24:2 or Octopus	**Reasons for withdrawals (dropouts)**	**Groups1 & 2:** • Inadequate IOP control = 1 • Repeated corneal erosions = 1 • Retinal arterial embolus = 1 • Retinal vein thrombosis = 1 • Increase in iris pigmentation = 1 • Information about iris changes = 2 • Decrease in visual acuity due to diabetes = 1 • Burning sensation on tongue = 1 • Cancer metastasis = 1 • Unknown reason for exit = 4 **Group 2:** • Inadequate IOP control = 1 • Information about iris changes = 3 • Headaches = 1	correlation coefficients calculated from Martin 2007[93] (bimatoprost) Computer generated randomisation sequence.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Camras, 1996[17] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG & OHT **Setting:** multi-centre 17 centres across the USA **Inclusion criteria:** • Age ≥ 40 years old • Unilateral or bilateral POAG or pigmentary glaucoma or exfoliation glaucoma or OHT ≥ 22 mmHg with no more than 1 current topical medication • Expectation that patients' IOP would be controlled for 6 months without VF degeneration • Completion of adequate washout period for sympathomimetics, CAI and miotics. **Exclusion criteria:** • Use of any ocular medications other than for glaucoma • Patients with advanced glaucoma that would be at risk during washout period • Angle closure glaucoma history • Ocular trauma • Previous filtration or laser surgery for glaucoma within 6 months of study • Allergies to trial medications • Ocular inflammation or infection within 3 months of study • Contact lens wearers • Those with contraindications for beta blockers • Pregnant women, women of	**Group 1** Latanoprost 0.005% in evening preceded by placebo in morning for 6 months **Group 2** Timolol 0.5% 2/day for 6 months **Examination methods:** IOP measured using Goldmann tonometer taking 3 replicate measurements on same calibrated machine per patient for each visit at 8am, 12 noon and 4 pm VF measured on Humphrey or Octopus 4 weeks before start of study at 6 month stage.	**Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)**	**Group 1:** 6.7 ± 3.4 **Group 2:** 4.9 ± 2.9 **p value:** <0.001 (using 2 tailed unpaired t-test)	**Funding:** Supported by Pharmacia (now Pfizer), Sweden which manufactures latanoprost **Limitations:** Allocation concealment with sealed envelopes was not reported. Lack of reliable ITT data in original study. Assumption that later study figures are reliable **Additional outcomes:** Study reports in detail on conjunctival hyperaemia **Notes:** For patients with 2 eyes eligible – mean IOP value was used for all calculations Computer generated randomisation sequence. Patients and examiners were kept masked to treatment allocation.
			Apparent deterioration or visual field	**Group 1:** 1 **Group 2:** 1	
			Number of patients with local ocular side effects	**Group1:** 71 **Group 2:** 101 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation	**Group 1:** 1 **Group 2:** 0	
			Number of patients with cardiovascular systemic side effects	**Group1:** 26 **Group 2:** 33 Includes upper respiratory tract infection, palpitations, shortness of breath, syncope	
			Reasons for withdrawals (dropouts)	**Group1:** • Local side effects = 2 (including allergic blepharoconjunctivitis • Systemic effects = 4 (including palpitations, peptic ulcer symptoms and 2 patients with maculopapular rash) • Non medical reasons = 4 (including left area, lost to follow-up, time constraints) **Group 2:** • Inadequate IOP control = 4 • Local side effects = 2 (including swelling of eyelids and allergic conjunctivitis) • Systemic effects = 4 (including	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	child bearing potential & nursing mothers • History of non-compliance **<u>All patients</u>** **N:** 268 **M/F:** 114/154 **Drop outs:** 20 **OHT:** 44 **COAG:** 50 **Black:** 65 **Non-black:** 203 **<u>Group 1</u>** **N:** 128 **Age (mean):** 61 ± 12 (30-89) **M/F:** 58/70 **Drop outs:** 10 **OHT:** 80 **COAG:** 48 **Black:** 27 **Non-black:** 101 **<u>Group 2</u>** **N:** 140 **Age (mean):** 63 ± 11 (33-90) **M/F:** 56/84 **Drop outs:** 10 **OHT:** 90 **COAG:** 50 **Black:** 38 **Non-black:** 102			palpitations, shortness of breath followed by bypass surgery, post mastectomy) • Non medical reasons = 1 patient left study without explanation	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Fellman et al., 2002[44] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG & OHT **Setting:** Multi-centre (44 sites) USA **Inclusion criteria:** • Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Age ≥ 21 • IOP 24-36 mmHg in same eye on 2 separate eligibility visits • Women post menopausal or surgically sterilised **Exclusion criteria:** • Contact lens wearers • Women of childbearing potential • IOP >36mmHg • Visual acuity worse than 0.60 log MAR • Cup/disc ratio > 0.80 • Chronic or recurrent inflammatory eye disease • Ocular trauma in last 6 months • Recent ocular infection or inflammation • Ocular pathology preventing beta blockers or PGAs • Recent ocular surgery • Contraindications for beta blockers – respiratory, cardiovascular, hepatic, renal • Patients on adjunctive IOP lowering therapies, glucocorticoids or NSAIDS • Patients with hypersensitivities to the medications	**Group 1** Travoprost 0.004% evening, placebo in morning **Group 2** Timolol 0.5% 2/day **Examination methods:** 2 different individuals performed IOP measurements on a Goldmann Tonometer. Hyperaemia was made by same observer throughout study looking at photographs depicting ocular hyperaemia. Photographs were taken to record iris pigmentation or eyelash characteristics. VF evaluation using Humphrey or Octopus	**Mean baseline diurnal IOP ± SD**	**Group 1:** 25.9 ± NR **Group 2:** 26.2 ± NR	**Funding:** Alcon Research Ltd which manufactures Travoprost. Dr Fellman has no proprietary interest in any of the medications **Limitations:** **Additional outcomes:** Detailed analysis of conjunctival hyperaemia **Notes:** *withdrawals due to adverse effect of treatment includes non-starters randomised to treatment 3rd arm of travoprost 0.001% not reported here ** Standard Deviations (SD) calculated as pooled variances from known SDs for Camras 1996[17], Martin 2007[93]and
			Mean change in IOP from baseline at 6 months	**Group 1:** 7.1 (8am), 6.6 (10am), 6.5 (4pm) **Group 2:** 6.8 (8am), 6.3 (10am), 5.2 (4pm)	
			Mean change in IOP from baseline mmHg at 6 months (end point – baseline	**Group 1:** 6.73 ± 6.87** **Group 2:** 6.1 ± 4.83** (IOP calculated as mean across 3 times)	
			% patients achieving acceptable target of >25% reduction in IOP over all visits (ITT) *>25% reduction from baseline is equivalent to mean IOP of ≤ 20 mmHg averaged over 3 time points*	**Group 1:** 113/197 (57%) **Group 2:** 79/199 (40%) Patient numbers rounded up.	
			Changes in visual field (baseline visit compared to exit visit)	Study reports no significant differences between treatment groups – actual data NR	
			Number of patients with local ocular adverse events	**Group 1:** 152 **Group 2:** 58 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation & Eyelash changes	**Group 1:** = 104 **Group 2:** = 4	
			Number of patients with cardiovascular systemic side effects	**Group 1:** = NR **Group 2:** = NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	<u>All patients</u> **N:** 396 (excludes non starters – those that did not attend treatment visits and travoprost 0.00015% not given at this concentration) **<u>Group 1</u>** **N:** 197 **Age (mean ±SD):** 64.4 ± 10.2 **M/F:** 94/103 **OHT**: 61 **COAG**: 136 **Black:** 17 **Non-Black:** 180 **Drop outs:** 9/201 (4.48%)* see notes **<u>Group 3</u>** **N:** 199 **Age (mean ±SD):** 63.9 ± 11.2 **M/F:** 64/105 **OHT**: 71 **COAG**: 128 **Black:** 23 **Non-Black:** 176 **Drop outs:** 2/202 (0.99%)* see notes		**Reasons for withdrawals (dropouts)**	**<u>Group 1</u>** • 9 includes local ocular effects and systemic effects including arrhythmia and **<u>Group 2</u>** • 1 dizziness, asthaenia & ocular discomfort • 1 bradycardia, hypotension and dizziness	Mastropasqua 1999[95] Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Goldberg et al., 2001[47] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 9 months	**Patient group:** COAG & OHT **Setting:** multi-centre 64 sites. Europe + Australia **Inclusion criteria:** • Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Age ≥ 21 • IOP 24-36 mmHg in same eye on 2 separate eligibility visits • Women post menopausal or surgically sterilised **Exclusion criteria:** • Women of childbearing potential • Visual acuity worse than 0.60 log MAR • Cup/disc ratio > 0.80 • Abnormalities preventing applanation tonometry • Severe central field loss: sensitivity <10dB • Chronic or recurrent inflammatory eye disease • Ocular trauma in last 6 months • Recent ocular infection or inflammation • Ocular pathology preventing beta blockers or PGAs • Recent ocular surgery within 3 mths • Contraindications for beta blockers – respiratory, cardiovascular, hepatic, renal	**Group 1** Travoprost 0.004% 1/day evening, placebo in morning **Group 2** Timolol 0.5% 2/day **Examination methods:** IOP measurements made at 9am. 11 am and 4 pm using Goldmann applanation tonometry. Photographs were taken to record iris pigmentation or eyelash characteristics and assessed by 2 independent analysts, with a third to resolve differences. VF evaluation using Humphrey or Octopus Hyperaemia assessed by visual inspection using scale. Aqueous flare and inflammatory cells assessed using slit lamp	**Mean IOP at baseline** (data requested from author)	**Group 1:** 27.4 ± 2.85 (9am), 26.4 ± 3.04 (11am), 25.5 ± 3.18 (4pm) **Group 2:** 27.1 ± 2.88 (9am), 26.2 ± 2.91 (11am), 25.1 ± 2.67 (4pm)	**Funding:** Alcon Research Ltd which manufactures Travoprost **Limitations:** Reasons for dropouts NR **Additional outcomes:** **Notes:** **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost) Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation
			Mean IOP at baseline (using 11 am reading)	**Group 1:** 26.4 ± 3.04 **Group 2:** 26.2 ± 2.91 (calculated as mean across 3 times)	
			Mean IOP at end point (9 months) (data requested from author)	**Group 1:** 18.9 ± 3.59 (9am), 18.0 ± 3.30 (11am), 17.6 ± 3.05 (4pm) **Group 2:** 19.4 ± 3.56 (9am), 18.8 ± 3.42 (11am), 18.7 ± 3.67 (4pm)	
			Mean IOP at end point (9 months) (using 11 am reading)	**Group 1:** 18.0 ± 3.30 **Group 2:** 18.8 ± 3.42 (calculated as mean across 3 times)	
			Mean change in IOP from baseline at 9 months	**Group 1:** 8.5 (9am), 8.4 (11am), 8.0 (4pm) **Group 2:** 7.6 (9am), 7.4 (11am), 6.4 (4pm) **p value** using least-square mean is <0.0001 at all time points	
			Mean change in IOP from baseline mmHg at 9 months (end point –baseline) (using 11 am reading)	**Group 1:** 8.4 ± 3.84** **Group 2:** 7.4 ± 3.46**	
			% patients achieving acceptable target IOP ≤ 20mmHg (not ITT data) *Figures estimated from graph and averaged over 3 time points*	**Group 1:** 161/176 **Group 2:** 133/163	
			Number of patients with local ocular adverse events reported at incidence of >1%	**Group 1:** 107 **Group 2:** 22 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema,	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	• Patients on adjunctive IOP lowering therapies, glucocorticoids • Patients with hypersensitivities to the medications • Patients that could not be safely discontinued from current ocular hypertensive medications **<u>All patients</u>** **N:** 382 **<u>Group 1</u>** **N:** 197 **Age (mean ± SD):** 63.0 ± 10.3 **M/F:** 96/101 **OHT**: 74 **COAG**: 123 **Black:** 2 **Non-Black:** 195 **Drop outs:** 9 **<u>Group 2</u>** **N:** 185 **Age (mean ±SD):** 62.5 ± 10.6 **M/F:** 96/89 **OHT**: 73 **COAG**: 112 **Black:** 2 **Non-Black:** 183 **Drop outs:** 3			dry eye and conjunctival hyperaemia	
			Increase in iris pigmentation & Eyelash changes	**Group 1:** = 10 **Group 2:** = 0	
			Number of patients with cardiovascular systemic side effects	**Group 1:** = NR **Group 2:** = NR	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Higginbotham et al., 2002[61] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months (double masked RCT part of study) Study continued for a further 6 months as an open-label study with everyone receiving the fixed combination treatment.	**Patient group:** COAG or OHT **Setting:** multi-centre (38 eye clinics) USA **Inclusion criteria:** • Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Aged 18 or older • Best corrected visual acuity measuring 20/200 • Pre-study IOP ≥30mmHg without IOP reducing medication OR ≥25mmHg with prior treatment • Previous latanoprost or timolol therapy permitted **Exclusion criteria:** • History of acute angle-closure or occludable angles • Use of contact lenses • Ocular surgery, argon laser trabeculoplasty or ocular inflammation or infection within 3 months of the pre-study visit • Hypersensitivity to benzalkonium chloride • Any other abnormal ocular condition or symptom that investigator determined precluded study enrolment • Presence of concomitant diseases that contraindicate adrenergic antagonist • Nursing mothers, pregnant women and women who were of	**Group 1** Fixed combination of Latanoprost 0.005% & timolol 0.5% 8am AND placebo 8pm **Group 2** Latanoprost 0.005% 8am AND placebo 8pm **Group 3** Timolol 0.5% 8am AND 8pm **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer. Each measurement taken in triplicate in each eye. Measurements taken at 8am, 10am and 4pm at baseline and weeks 2, 13, 26 and 52. Automated visual field examination performed at baseline and weeks 13, 26 and 52.	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 23.1 ± 3.8 **Group 2:** 22.9 ± 4.1 **Group 3:** 23.7 ± 4.1	**Funding:** Pharmacia & Upjohn Inc.; Research to Prevent Blindness Inc. **Limitations:** Run in period 2 – 4 weeks with timolol 0.5 % 2/day prior to starting study Adverse events reported by area of eye they occur making it difficult to assess total no. of patients with a particular event. **Notes:** *Differences estimated (least square mean difference) using a repeated measures analysis of covariance with baseline IOP as a covariate; patient, treatment, visit and centre as main factors; and treatment group-by-visit and treatment group-by-centre interaction factors. § values not reported for group 2 to group 3 Intention to treat analysis for the first 6 months included all patients who received at least one drop of medication. For IOP measurements the last
			Mean ± SD diurnal IOP at 6 mths mmHg	**Group1:** 19.9 ± 3.4 **Group 2:** 20.8 ± 4.6 **Group 3:** 23.4 ± 5.4	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths §	**Group1 to Group 3:** -2.9 (95% CI: -3.5 to -2.3, p<0.001)* **Group 1 to Group 2:** -1.0 (95% CI: -1.7 to -0.3, p=0.005)*	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths	**Group 2:** 2.1 ± 5.27** **Group 3:** 0.3 ± 5.27**	
			Percent of patients reaching IOP <15mmHg at of 6 mths §	**Group1:** 6 /130 **Group 2:** 4/128 **Group 3:** 1/129 **P value (group 1 to 3):** 0.06 **P value (group 1 to 2):** 0.56	
			Percent of patients reaching IOP acceptable IOP <18mmHg at of 6 mths § *figures used in meta-analysis*	**Group1:** 28/130 **Group 2:** 30/128 **Group 3:** 8/129 **P value (group 1 to 3)** =0. 01 **P value (group 1 to 2)** =0. 65	
			Percent of patients reaching IOP <21mmHg at of 6 mths §	**Group1:** 68/130 **Group 2:** 63/128 **Group 3:** 39/129 **P value (group 1 to 3)** <0.001 **P value (group 1 to 2)** =0.36	
			Number of ocular side effects †	**Group1:** 86 **Group 2:** 86 **Group 3:** 59 † side effects include belphartis,	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	childbearing potential not using adequate contraception for at least the previous 3 months • Patients who could not adhere to treatment or the visit plan • Patients who had participated in another clinical study within 1 month of previous visit **<u>All patients</u>** **N:** 418 **Age (mean):** NR **M/F:** 215/203 **Drop outs:** 73 **Ethnicity:** white 276, black 110, Hispanic 27, other 5 **Diagnosis:** POAG 278, pseudoexfoliative glaucoma 9, pigmentary glaucoma 13, OHT 109, mixed (different diagnosis in the two eyes) 8, none listed 1 **IOP reducing medication in last 3 months:** 351/418 **<u>Group 1</u>** **N:** 138 **Age (mean):** 61 ±12 **M/F:** 67/71 **Drop outs:** 13 **Ethnicity:** white 90, black 38, Hispanic 7, other 3 **Diagnosis:** POAG 94, pseudoexfoliative glaucoma 2, pigmentary glaucoma 4, OHT 36, mixed 2, none listed 0 **IOP reducing medication in last 3 months:** 117/138	Visual acuity assessed and eye-lid slit lamp biomicroscopy performed at each visit. Ophthalmoscopy performed at pre-study visit and weeks 26 and 52.		hypertrichosis, irritation, melbomianitis, seborrhea, eye hyperaemia, chemosis, conjunctival discolouration, corneal disorder, keratitis, keratopathy, cataract, optic atrophy, errors of refraction, increased IOP, vision decreased, visual field defect, conjunctivitis, epiphora, eye pain, photophobia, vision blurred	available IOP measurement was carried forward. **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost) Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation
			Visual field defects	**Group1:** 7/130 **Group 3:** 4/128	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 140 **Age (mean):** 63 ±13 **M/F:** 80/60 **Drop outs:** 36 **Ethnicity:** white 90, black 35, Hispanic 14, other 1 **Diagnosis:** POAG 95, pseudoexfoliative glaucoma 4, pigmentary glaucoma 5, OHT 33, mixed 3, none listed 0 **IOP reducing medication in last 3 months:** 117/140 **Group 3** **N:** 140 **Age (mean):** 63 ±12 **M/F:** 68/72 **Drop outs:** 24 **Ethnicity:** white 96, black 37, hispanic 6, other 1 **Diagnosis:** POAG 89, exfoliative glaucoma 3, pigmentary glaucoma 4, OHT 40, mixed 3, none listed 1 **IOP reducing medication in last 3 months:** 117/140				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Martin et al., 2007[93] **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG & OHT **Setting:** single centre, Spain **Inclusion criteria:** • Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT in at least one eye • Age > 18 • IOP ≥ 22 mmHg at enrolment and between 24-34 mmHg after washout. • Visual acuity ≥ 0.1 in study eye • Completion of adequate washout period for Sympathomimetics, CAI and miotics. **Exclusion criteria:** • Infection or inflammation of the eye • Any anomaly impeding tonometry • History of contraindications for any treatments • Macular or retinal pathologies • Diabetes • Women of childbearing potential not using contraception • Requirement for other chronic eye medication during the study • Eye surgery 6 mths previously • Laser treatment 3 mths previously **<u>All patients</u>** **N:** 60 **Age (mean):** NR **M/F:** NR **Drop outs:** 0	**Group 1** Bimatoprost 0.03% 1/day at 9pm **Group 2** Timolol 0.5% 2/day **Examination methods:** Applanation tonometry Macular tomography using OCT 3000 Anterior flare determination using laser flare meter	**Mean ± SD baseline diurnal IOP mmHg**	**Group 1:** 24.1 ± 3.2 **Group 2:** 24.1 ± 1.7	**Funding:** Partly financed by the Instituto de Salud Carlos III. Authors declare no commercial interests. **Limitations:** Author reports that the study was not sponsored so allocation concealment was not possible and masking of patients not possible. This may effect self-reporting of adverse events but outcome assessment was performed by an ophthalmologist masked to treatment allocation. Baseline data not reported **Additional outcomes:** Inter or intra group differences in macular thickness not significant Inter or intra group differences in anterior chamber flare not significant **Notes:** No patients discontinued study due to adverse events
			Mean ± SD end point diurnal IOP (6 mths) mmHg	**Group 1:** 13.5 ± 3.1 **Group 2:** 16.6 ± 2.4 **p value** compares difference in end point IOP between groups, p is 0.003 using ANOVA for repeated measures	
			Mean ± SE reduction in diurnal IOP mmHg at 6 mths (baseline – end point)	**Group1:** 10.7 ± 3.8 **Group 2:** 7.6 ± 2.3	
			Proportion of patients reaching acceptable target IOP of ≤18mmHg *Figures estimated from graph*	**Group 1:** 17/30 **Group 2:** 28/30	
			Conjunctival hyperaemia	**Group 1:** 4 **Group 2:** 0	
			Increase in iris pigmentation & Eyelash changes	**Group 1:** 3 **Group 2:** 0	
			Number of patients with cardiovascular systemic side effects	**Group 1:** = NR **Group 2:** = NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 30 **Age (mean):** NR **M/F:** NR **Drop outs:** 0 **Group 2** **N:** 30 **Age (mean):** NR **M/F:** Nr **Drop outs:** 0				Computer generated randomisation sequence. Outcome assessment was masked.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Mastropasqua et al., 1999[95] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** Pigmentary Glaucoma **Setting:** single centre, Italy **Inclusion criteria:** • Untreated IOP > 21 mmHg • Evidence of optic nerve head change and VF changes • Best corrected visual acuity ≥ 15/20 – no media opacities • Refractive errors not exceeding -8 or +6D • MD Humphrey not exceeding -12.0dB • Discontinuation of previous glaucoma treatments of 4 weeks **Exclusion criteria:** • History of ocular, rhinologic, neurologic or systemic disorders accounting for optic nerve head damage • History of haemodynamic crisis • Previous surgery or laser treatment in either eye **<u>All patients</u>** **N:** 36 **Age (mean):** NR **M/F:** 21/15 **Drop outs:** 2 **Race:** NR **Family history:** 9 **<u>Group 1</u>**	**Group 1** Latanoprost 0.005% 1/day 8 pm with placebo am **Group 2** Timolol 0.5% 2/day **Examination methods:** Goldmann applanation tonometer used to measure IOP. Average of 3 readings taken at each time interval: 8am, 12 noon, 4pm, 8pm. Outflow facility measured with a Scholtz electronic tonometer at baseline and at end point of study.	**Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)** **Mean ± SD reduction in diurnal IOP mmHg at 12 months (baseline – end point)** **Total number of ocular side effects experienced at least once in 1 year*** **Increase in iris pigmentation** **Reasons for withdrawals (dropouts)**	**Group1:** 6.0 ± 4.5 **Group 2:** 4.8 ± 3.0 **Group1:** 5.9 ± 4.6 **Group 2:** 4.6 ± 3.1 **Group1:** 24 **Group 2:** 35 Includes itching, stinging, conjunctival hyperaemia & dry eye **Group1:** 3 **Group 2:** 0 **Group1:** moved away = 1 **Group 2:** inadequate IOP control = 1	**Funding:** Funding details not clear but study conducted at Institute of Ophthalmology, University "G D'Annunzio", Chieti, Italy **Limitations:** Small study. **Additional outcomes:** Aqueous outflow facility (C) measured at baseline and after 1 year. µl/min/mmHg Detailed analysis of conjunctival hyperaemia **Notes:** Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 18 **Age (mean ± SD):** 46.1 ± 9.9 **M/F:** 10/8 **Family history:** 4 **Drop outs:** 1 **Group 2** **N:** 18 **Age (mean ± SD):** 45.8 ± 10.5 **M/F:** 11/7 **Family history:** 5 **Drop outs:** 1				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Netland et al., 2001[110] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** COAG & OHT **Setting:** Multi-centre USA **Inclusion criteria:** • Diagnosis of POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • IOP 24 - 36mmHg in same eye on 2 separate eligibility visits • Women post menopausal or surgically sterilised **Exclusion criteria:** • Contact lens wearers • Women of childbearing potential • IOP >36mmHg • Visual acuity worse than 0.60 log MAR • Chronic or recurrent inflammatory eye disease • Ocular trauma in last 6 months • Recent ocular infection or inflammation • Ocular pathology preventing beta blockers or PGAs • Cup/Disc ratio >0.80 • Recent ocular surgery • Contraindications for beta blockers – respiratory, cardiovascular, hepatic, renal • Patients on adjunctive IOP lowering therapies **<u>All patients</u>** **N:** 585	**Group 1** Travoprost 0.004% evening, placebo in morning **Group 2** Timolol 0.5% 2/day **Group 3** Latanoprost 0.005% evening, placebo in morning **Examination methods:** 2 different individuals performed IOP measurements on a Goldmann Tonometer. Hyperaemia was made by same observer throughout study looking at photographs depicting ocular hyperaemia. Photographs were taken to record iris pigmentation or eyelash characteristics. VF evaluation using Humphrey	**Mean baseline diurnal IOP ± SD**	**Group 1:** 25.5 ± NR **Group 2:** 25.7 ± NR **Group 3:** 25.7 ± NR	**Funding:** Alcon Research Ltd which manufactures Travoprost. **Limitations:** Study provides detailed baseline data on 585 patients but excludes those that were randomised but never started trial. However adverse events % includes patients who never started trial **Additional outcomes:** Detailed analysis of conjunctival hyperaemia **Notes:** *No discontinuations due to adverse events were reported but dropout numbers refer to those that were randomised into the trial but failed to start treatment.
			Mean change in IOP from baseline at 12 mths	**Group 1:** 5.8 (8am), 7.3 (10am), 7.6 (4pm) **Group 2:** 5.0 (8am), 5.8 (10am), 5.8 (4pm) **Group 3:** 6.3 (8am), 7.6 (10am), 7.1 (4pm)	
			Mean change in IOP from baseline mmHg at 12 months (end point – baseline	**Group 1:** 6.9 ± 6.87** **Group 2:** 5.53 ± 4.83** **Group 3:** 7.0 ± 6.87** (calculated as mean across 3 times)	
			Mean diurnal change in IOP from baseline mmHg (expressed as a range)	**Group 1:** 6.6 – 8.1 **Group 2:** 4.7 – 7.1 **Group 3:** 6.2 – 8.1 **p value** compares difference between travoprost 0.004% and Timolol using ANOVA for repeated measures. p is <0.01 at all time points	
			Proportion of patients reaching acceptable target IOP of >30% reduction from baseline or ≤17 mmHg *Patient numbers unclear so numbers randomised used for denominator*	**Group 1:** 108/197 **Group 2:** 75/193 **Group 3:** 97/195	
			Total number of patients with local ocular adverse events reported at incidence of >3%	**Group 1:** 219 **Group 2:** 93 **Group 3:** 121 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 197 **Age (mean ±SD):** 64 ± 13.3 **M/F:** 100/97 **OHT:** 67 **COAG:** 130 **Black:** 49 **Non-Black:** 148 **Drop outs:** 3 *see notes **Group 2** **N:** 195 **Age (mean ±SD):** 64.8 ± 11.6 **M/F:** 107/88 **OHT:** 55 **COAG:** 140 **Black:** 40 **Non-Black:** 155 **Drop outs:** 5 *see notes **Group 3** **N:** 193 **Age (mean ±SD):** 64.5 ± 11.6 **M/F:** 89/104 **OHT:** 59 **COAG:** 134 **Black:** 43 **Non-Black:** 150 **Drop outs:** 3 * see notes		**Increase in iris pigmentation & Eyelash changes**	**Group 1:** 118 **Group 2:** 6 **Group 3:** 60	** Standard Deviations (SD) calculated as pooled variances from known SDs for Camras 1996[17], Martin 2007[93] and Mastropasqua 1999[95] Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation.
			Number of patients with cardiovascular systemic side effects reported at incidence of >3%	**Group 1:** 13 **Group 2:** 9 **Group 3:** 7 Includes hypertension	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pfeiffer, 2002[116] European Latanoprost Fixed Combination Study Group **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months Plus a 6 month open-label study with all patients using the fixed combination of latanoprost and timolol	**Patient group:** COAG or OHT **Setting:** multicentre - 37 centres, Germany **Inclusion criteria:** • Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Aged 18 or older • IOP ≥25mmHg with prior therapy • IOP ≥30mmHg without prior therapy **Exclusion criteria:** • History of angle-closure glaucoma • Previous ocular surgery, argon laser trabeculoplasty or ocular inflammation or infection 3 months prior to pre-study visit • Patients with a known hypersensitivity or contraindication to any component of study drugs **All patients** **N:** 436 **Age (mean):** NR **M/F:** 196/240 **Drop outs:** 72 **Ethnicity:** NR **Diagnosis: :** POAG 336, pseudoexfoliative glaucoma 22, pigmentary glaucoma 8, ocular hypertension 64, mixed (different	**Group 1** Fixed combination of latanoprost 0.005% & timolol 0.5% am, placebo pm **Group 2** Latanoprost 0.005% 1/day am, placebo pm **Group 3** Timolol 0.5% 2/day **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer at pre-study visit. Method of measurement for other visits not stated. Each measurement taken three times in each eye. Measurements for each visit taken at 8am, 10am and 4pm. Also determined at	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 21.6 ± 3.8 **Group 2:** 22.5 ± 4.0 **Group 3:** 22.5 ± 4.1	**Funding:** Pharmacia Inc **Limitations:** Adverse events poorly reported. Randomisation method and allocation concealment were not reported. Although patients were masked it is not clear whether examiners were masked. **Additional outcomes:** Also reported mean diurnal IOP at week 2 and 13; no. of patients switching to open-label trial on fixed combination. **Notes:** † Reported ocular adverse events: eye irritation, visual field change (suspected), hypertrichosis, hyperaemia, vision decreased, increased iris pigmentation, corneal disorder, cataract, optic atrophy, conjunctivitis, iritis, change in refraction, blepharitis. Gives number of patients for each adverse event. **§** Reported non-ocular adverse
			Mean ± SD diurnal IOP at 6 mths mmHg	**Group1:** 19.0 ± 3.5 **Group 2:** 20.4 ± 4.9 **Group 3:** 21.4 ± 5.4 **P values:** not reported	
			Mean ± SD reduction in diurnal IOP at 6 mths	**Group 1:** 1.7 ± 3.36** **Group 2:** 2.1 ± 5.42** **Group 3:** 1.1 ± 5.27**	
			Percent of patients reaching IOP <15mmHg at 6 mths or up to treatment failure	**Group1:** 14/140 **Group 2:** 8/147 **Group 3:** 7/149 **P values:** not significant	
			Percent of patients reaching acceptable IOP <18mmHg at 6 mths or up to treatment failure *Used in met-analysis*	**Group1:** 54/140 **Group 2:** 48/147 **Group 3:** 37/149 **P values:** Group 1 to 3 p<0.05	
			Percent of patients reaching IOP <21mmHg at 6 mths or up to treatment failure	**Group1:** 110/140 **Group 2:** 101/147 **Group 3:** 83/149 **P values:** not significant	
			No. of ocular adverse events by group seen in ≥1% of any treatment group (NB not no. of patients) §	**Group1:** 34 **Group 2:** 41 **Group 3:** 21	
			No. of non-ocular adverse events by group seen in ≥1% of any treatment group (NB not no. of patients) §	**Group1:** 22 **Group 2:** 18 **Group 3:** 19	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	diagnosis in the two eyes) 6 **Previous IOP reducing medication**: 401 **Group 1** **N:** 140 **Age (mean):** 64 ±13 **M/F:** 67/73 **Drop outs:** 12 **Ethnicity:** NR **Diagnosis:** POAG 106, pseudoexfoliative glaucoma 2, pigmentary glaucoma 3, ocular hypertension 27, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication**: NR **Group 2** **N:** 147 **Age (mean):** 63 ±12 **M/F:** 77/70 **Drop outs:** 28 **Ethnicity:** NR **Diagnosis:** POAG 112, pseudoexfoliative glaucoma 13, pigmentary glaucoma 4, ocular hypertension 16, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication in last**: NR **Group 3** **N:** 149 **Age (mean):** 64 ±10 **M/F:** 52/97 **Drop outs:** 32 **Ethnicity:** NR **Diagnosis:** POAG 118, pseudoexfoliative glaucoma 7,	each visit: best corrected visual acuity and slit lamp examination. Refraction recorded, ophthalmoscopy performed and Colour Polaroid photographs taken at 6 months.	**No. of patients not completing 6 months in randomised group** * **No. of patients not completing 6 months in randomised group OR in open label trial**	**Group1:** 12/140 **Group 2:** 28/147 **Group 3:** 32/149 **P value group 1 to 2:** =0.006 **P value group 1 to 3:** =0.001 **P value group 2 to 3:** =0.10 **Group1:** 10/140 **Group 2:** 14/147 **Group 3:** 16/149 **P values:** not significant	events: cardiovascular disorder, influenza-like symptoms, metabolic disorders, respiratory disorders, cerebrovascular disorders, vertigo, sleep disorders, headache, liver/biliary disorders Patients switched medications to the fixed combination used in for group 1 if treatment failure occurred. Treatment failure defined as increased IOP ≥10% of the mean IOP from baseline and an IOP of ≥23mmHg on two examinations within 2 weeks. Study reports numbers by group. If treatment still did not work patients were withdrawn. **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	pigmentary glaucoma 1, ocular hypertension 21, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication in last:** NR				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Tomita et al., 2004[150] **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 3 years	**Patient group:** Normal tension glaucoma **Setting:** multi-centre (3 sites) Japan **Inclusion criteria:** • Untreated IOP ≤ 21 mmHg • Evidence of optic nerve head change and VF changes • Best corrected visual acuity ≥ 15/20 – no media opacities • Refractive errors not exceeding -8 or +6D • MD Humphrey not exceeding -12.0dB • Discontinuation of previous glaucoma treatments of 4 weeks **Exclusion criteria:** • History of ocular, rhinologic, neurologic or systemic disorders accounting for optic nerve head damage • History of haemodynamic crisis • Previous surgery or laser treatment in either eye **<u>All patients</u>** **N:** 62 **Age (mean):** NR **M/F:** **Drop outs:** 15 (24%) **<u>Group 1</u>**	**Group 1** Latanoprost 0.005% 1/day **Group 2** Timolol 0.5% 2/day **Examination methods:** Average of 2 IOP measurements adopted for baseline IOP. Goldmann tonometry used. Subsequent IOP measurements were taken every month at 9am before morning dose. Humphrey perimetry used for visual field defects every 6 months. If VF measurement did not meet reliability criteria it was repeated after 1 month. Abnormal VF at least 3 adjacent test points. Stereoscopic optic disc photographs taken every 6 months and analysed using 3D image analysis programme.	**Mean ± SD baseline IOP mmHg**	**Group1:** 15.0 ± 1.6 **Group 2:** 15.9 ± 2.0	**Funding:** Funding NR but study conducted by Dept Ophthalmology, University of Tokyo. Gifu University of Medicine and Yamanashi University School of Medicine. **Limitations:** Open label study **Additional outcomes:** **Notes:** No data on adverse events Randomly assigned to groups using a computer generated list kept in a sealed envelope. Optic disc stereophotographs were analysed by a masked observer. **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost)
			Mean ± SD end point IOP (3 years) mmHg	**Group1:** 12.9 ± 2.2 **Group 2:** 14.0 ± 2.0	
			Mean ± SD reduction in IOP mmHg at 6 mths (baseline – end point)	**Group1:** 2.1 ± 2.35** **Group 2:** 1.9 ± 2.17** **p value** NR not signif at any time point using repeated measure ANOVA	
			% reduction both groups	**13-15%** **p value** NR not signif at any time point using repeated measure ANOVA or t test	
			Mean ± SD baseline Mean deviation for VF dB	**Group1:** -6.0 ± 2.1 **Group 2:** -5.9 ± 2.3	
			Mean ± SD end point Mean deviation for VF dB (3 years)	**Group1:** -6.3 ± 3.2 **Group 2:** -5.6 ± 2.9	
			Estimated rate of change of MD ± SE value/Year	**Group1:** -0.34 ± 0.17 **Group 2:** -0.10 ± 0.18 **p value:** Not signif.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 31 **Age (mean ± SD):** 56 ± 10 **M/F:** 14/17 **Drop outs:** 8 **<u>Group 2</u>** **N:** 31 **Age (mean ± SD):** 54.3 ± 8.5 **M/F:** 15/16 **Drop outs:** 7				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Vetrugno et al., 2004[156] **Study design:** RCT Unmasked **Evidence level:** 1 + **Duration of follow-up:** 6 months	**Patient group:** POAG only **Setting:** single centre, Italy **Inclusion criteria:** • Diagnosis of POAG • Age 40 - 60 • Non smokers • IOP < 16 mmHg after 12 months pre treatment with timolol • Refraction ± 3 D ≥ 0.1 in study eye • > 10% reduction of pulsatile ocular blood flow pOBF after 12 months pre treatment with timolol • Systolic brachial pressure 120 – 140 mmHg • Diastolic brachial pressure 70-90 mmHg • Heart rate 66-80 bpm • BMI normal • Normal blood haemological test results **Exclusion criteria:** • Cardiovascular abnormalities (atherosclerosis, carotid stenosis) • Use of systemic vaso-active therapy (beta-blockers, Ca agonists, nitroglycerin derivatives) • Types of glaucoma other than POAG **<u>All patients</u>** **N:** 38	**Group 1** Bimatoprost 0.3 % 1/day 9pm **Group 2** Timolol 0.5% 2/day **Examination methods:** IOP and pOBF measured at 9am each study visit. pOBF measured on a tonograph but IOP measurement methods not reported	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 17.00 ± 1.69 **Group 2:** 16.75 ± 2.38	**Funding:** Author reports that the study is not funded by industry. **Limitations:** • The study is actually looking at the effect of bimatoprost on patients where their IOP has already been lowered effectively with timolol. • Open label study. Treatments were not masked - may affect reporting of adverse events. Outcome assessment was not masked either but same investigator carried out all the tests. • Small study **Additional outcomes:** pOBF mean ± SD **Notes:** No serious adverse events were noted in either group but adverse events were NR for timolol **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost)
			Mean ± SD end point diurnal IOP (6 mths) mmHg	**Group1:** 13.5 ± 1.31 **Group 2:** 15.75 ± 1.67	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)	**Group1:** 3.5 ± 1.84** **Group 2:** 1.0 ± 2.28** **p value** compares IOP at end point between groups (not reduction) p using unpaired t test is < 0.01	
			Conjunctival hyperaemia + itching	**Group 1:** 5 **Group 2:** 0	
			↑ periorbital pigmentation & Eyelash changes	**Group 1:** 2 **Group 2:** 0	
			Number of patients with cardiovascular systemic side effects	**Group 1:** = NR **Group 2:** = NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean ± SD): 51.7 ± 4.8 **M/F:** 22/16 **Race:** NR **Drop outs:** 0 **Group 1** **N:** 19 **Age (mean ± SD):** 52.1 ± 5.01 **M/F:** 12/7 **Drop outs:** 0 **Group 2** **N:** 19 **Age (mean ± SD):** 51.2 ± 4.12 **M/F:** 10/9 **Drop outs:** 0				Computer generated randomisation sequence.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Watson & Stjernschantz, 1996[158] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG & OHT **Setting:** Multi-centre – 14 centres, UK **Inclusion criteria:** • Age ≥ 40 years old • Unilateral or bilateral POAG or pigmentary glaucoma or exfoliation glaucoma or OHT ≥ 22 mmHg. • Completion of adequate washout period for sympathomimetics, CAI and miotics. **Exclusion criteria:** • Patients on topical beta blockers within 6 months of study • Angle closure glaucoma history • Ocular trauma • Previous filtration or laser surgery for glaucoma within 6 months of study • Dry eye syndrome • Ocular inflammation or infection within 3 months of study • Contact lens wearers • Those with contraindications for beta blockers • Women of child bearing potential & nursing mothers • Patients who would not benefit from monotherapy **<u>All patients</u>** **N:** 294 **Age (mean):** 65 ± 10 **M/F:** 191/103 **Drop outs:** 26 (8.8%) **White:** 285	**Group 1** Latanoprost 0.005% 1/day pm + placebo am for 6 months **Group 2** Timolol 0.5% 2/day morning and evening for 6 months **Examination methods:** IOP measured by Goldmann Applanation Tonometry - 3 readings taken at each visit (9 am, 1 pm, 5 pm) and mean taken for statistical analysis. Blood and urine samples taken at baseline and last visit. Iris photography taken Visual Field analysis	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 25.2 ± 3.4 **Group 2:** 25.4 ± 3.6	**Funding:** Supported by Pharmacia (now Pfizer), Sweden which manufactures latanoprost **Limitations:** It is not clear whether analysis of IOP is calculated on an ITT basis. **Additional outcomes:** Detailed analysis of conjunctival hyperaemia **Notes:** **Standard Deviations (SD) calculated using the Cochrane method for imputed SDs from correlation coefficients calculated from Martin 2007[93] (bimatoprost) Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation.
			Mean ± SD end point diurnal IOP (6 mths) mmHg	**Group1:** 16.7 ± 2.6 **Group 2:** 17.1 ± 2.6	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)	**Group1:** 8.5 ± 3.68** **Group 2:** 8.3 ± 3.47** **p value** NR - not signif (using covariate analysis)	
			% reduction in IOP at end point of 6 mths	**Group1:** 33.7 **Group 2:** 32.7	
			Number of patients with local ocular side effects	**Group1:** 215 **Group 2:** 158 Includes itching, stinging, conjunctivitis, vision disturbance, corneal erosions, eyelid oedema, dry eye and conjunctival hyperaemia	
			Number of patients with ↑ iris pigmentation	**Group1:** 2 **Group 2:** 0	
			Number of patients with cardiovascular systemic side effects	**Group1:** 32 **Group 2:** 28 Includes respiratory infection, bronchitis, arterial hypotension, angina, shortness of breath	
			Reasons for withdrawals (dropouts)	**Group1:** • Inadequate IOP control = 2 • Local side effects = 2 • Breathing problems = 1 • Bad compliance/lost patient = 6 • Contraindicated prescription = 1 **Group 2:** • Breathing/respiratory problems = 3	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Black: 9 **<u>Group 1</u>** **N:** 149 **Age (mean):** 64.7 ± 9.5 **M/F:** 98/51 **Drop outs:** 12 **White:** 143 **Black**: 6 **OHT only**: 80 **COAG or COAG + OHT**: 69 **<u>Group 2</u>** **N:** 145 **Age (mean):** 65.3 ± 10.5 **M/F:** 93/52 **Drop outs:** 14 **White:** 142 **Black:** 3 **OHT only**: 68 **COAG or COAG + OHT**: 77			• Arterial hypotension/bradycardia = 2 • Headaches = 2 • Local side effects = 5 • Previous timolol = 1 • Self withdrawal = 1	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 7 Prostaglandin analogues vs. sympathomimetics

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Camras et al., 2005[18] **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** POAG and OHT patients **Setting:** Multi-centre 23 centres in the USA **Inclusion criteria:** • ≥ 18 years • Naïve to glaucoma therapy or on topical monotherapy • Best-corrected visual acuity ≥ 20/80 • IOP ≥ 22 mm Hg **Exclusion criteria:** • Closed/barely opened anterior chamber angle or history of acute angle closure • No history of Argon laser trabeculoplasty or any ocular surgery or inflammation/infection within the 3 months prior to pre-study visit **<u>All patients</u>** **N:** 303 **Mean IOP:** **Drop outs:** 57 (19%) **<u>Group 1 (reported as ITT group)</u>** **N:** 151 **Age (mean ± SEM):** 62 ± 1.0 **M/F:** 70/81	**Group 1** Latanoprost 0.005% once daily (8 am) for 6 months **Group 2** Brimonidine 0.2% twice daily 8 am and 8 pm) for 6 months **All** Washout period completed as appropriate <u>6 visits</u>: Screening Baseline Week 2 3 months 6 months Follow up Goldmann applanation tonometer to record IOP reading (8am, 10 am , 12 pm and 4 pm except week 2 visit only 8 am)	**Mean diurnal (8 am, noon and 4 pm) IOP at 6 months (mm Hg)**	**Group1:** 18.8 ± 0.3 (± SEM) **Group 2:** 21.5 ± 0.3 (± SEM) **p value:** p < 0.001 (significantly lower than corresponding baseline values)	**Funding:** Supported in part by Pharmacia corporation, a Pfizer company (New York) which manufactures latanoprost and an unrestricted grant from (University of Nebraska Medical Centre) from Research to Prevent Blindness Inc. (New York). **Limitations:** • Open label • Use of adjusted and unadjusted means very confusing. • High drop out rate >20% in Brimonidine group **Additional outcomes:** Percentage of patients achieving pre-specified IOP levels (e.g. ≥ 40%, ≥ 30%, ≥ 10% etc.) after 6 months of treatment **Notes:** Randomisation using computer generated
			Differences in mean diurnal change in IOP between groups: baseline to 6 months	**Mean:** 2.5 ± 0.3 (± SEM) **95% CI:** 1.9- 3.2 **p value:** p < 0.001 in favour of group 1 (latanoprost)	
			Adjusted mean diurnal change in IOP from baseline to 6 months	**Group1:** 5.7 ± 0.3 (± SEM) **Group 2:** 3.1 ± 0.3 (± SEM) **p value:** p < 0.001	
			Differences in mean diurnal change in IOP between groups: baseline to 6 months (Post hoc analyses including 10 am reading).	**Group 1:** 5.5 ± 0.3 (± SEM) **Group 2 :** 3.6 ± 0.3 (± SEM) **Difference in mean:** 2.0 ± 0.4 **95% CI:** 1.3- 2.6 **p value:** p < 0.001 in favour of group 1 (latanoprost)	
			Mean % reduction on diurnal IOP at month 6	**Group1:** 22.6% **Group 2:** 12.8% **95% CI:** NR **p value:** p < 0.001	
			Adverse events resulting in withdrawal from study	**<u>Any adverse event</u>** **Group 1:** 4/151 (3%) **Group 2:** 23/152 (15%) **p value:** p < 0.001 (Fisher's exact test) **<u>External ocular</u>** **Group 1:** 2/151 (1%) **Group 2:** 15/152 (10%) **p value:** p = 0.06 (Fisher's exact test) **<u>Central nervous system</u>**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Race: Caucasian 104 African American 36 Other 11 **Mean IOP ± SEM:** 24.6 ± 0.3 **Drop outs:** 21 (14% including 4 adverse events, 8 IOP not controlled, 2 lost to follow-up and 2 protocol violations) **<u>Group 2 (reported as ITT group)</u>** **N:** 150 **Age (mean ± SEM):** 64 ± 1.0 **M/F:** 77/73 **Race:** Caucasian 103 African American 39 Other 8 **Mean IOP ± SEM:** 24.8 ± 0.2 **Drop outs:** 36 (24% including 23 adverse events, 10 IOP not controlled, 2 lost to follow up, 1 protocol violation).			**Group 1:** 0 **Group 2:** 5/152 (3%) **p value:** p < 0.001 (Fisher's exact test) **<u>Dry mouth:</u>** **Group 1:** 0 **Group 2:** 1/152 (1%) **<u>Other</u>** (including palpitations, reduced visual acuity, blurred vision, increased lacrimation, diplopia) **Group 1:** 2/151 (2%) **Group 2:** 2/152 (1%)	allocation. Masked outcome assessment. Originally 303 patients (152/151) but 2 excluded and not considered in the ITT analysis (terminated after baseline and before instillation of treatment.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Prostaglandin analogues vs. sympathomimetics (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kampik et al., 2002[70] European latanoprost study group **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** POAG and OHT patients **Setting:** Multi-centre- 30 eye clinics in Germany, UK, Spain and Finland **Inclusion criteria:** • Age ≥ 18 years • Unilateral or bilateral POAG or exfoliation glaucoma or OHT with IOP of ≥ 21mm Hg with current monotherapy or dual therapy **Exclusion criteria:** • Previous treatment with latanoprost or brimonidine or ongoing treatment with α-adrenoceptor agonists • Closed or barely open anterior chamber angle or history of acute angle closure • Argon laser trabeculoplasty, filtering surgery or other ocular surgery within the last 3 months • Current use of contact lenses • Ocular inflammation or infection within the last 3 months • Known hypersensitivity to any of the eye drop components **<u>All patients</u>** **N:** 379 **Age (mean):** **M/F:** 154/225 **Mean IOP:** NR **Drop outs:** 52 (13.3%)	**Group 1** Latanoprost 0.005% once daily (10 pm) for 6 months **Group 2** Brimonidine 0.2% twice daily (8 am and 10 pm) for 6 months. **All** At least 4 weeks washout period 4 visits during 6 month study: Baseline 2 weeks 3 months 6 months 3 IOP measurements in each eye using Goldmann applanation tonometer taken at: - 10 am and 5 pm at baseline, 3 months and 6 months - Only before 12 noon at 2 weeks The mean of the 3 measurements was taken and if both eyes were study eyes the	**Mean ± SD diurnal IOP at baseline (mm Hg)**	**Group1:** 25.1 ± 3.7 **Group 2:** 24.9 ± 3.0	**Funding:** Supported by a research grant from Pharmacia Corporation (Peapack, NJ) manufacturers of latanoprost **Limitations:** • Open label • Randomisation method and allocation concealment was not reported. • Significantly higher number of OHT patients in group 1 compared to group 2 (p = 0.027) • **Additional outcomes:** Percentage of patients achieving prespecified IOP levels (e.g. ≤21, ≤20, ≤15 etc.) after 6 months of treatment **Notes:** Masked outcome assessment. Statistical analysis does not include the 4
			Mean ± SD diurnal IOP at 6 months (mm Hg)	**Group1:** 18.0 ± 2.9 **Group 2:** 19.8 ± 3.1	
			Mean ± SD diurnal change in IOP from baseline at 6 months (mm Hg)	**Group1:** 7.1 ± 3.3 **p value:** p < 0.001 (ANCOVA) **Group 2:** 5.2 ± 3.5 **p value:** p < 0.001 (ANCOVA)	
			% reduction in mean IOP from baseline	**Group1:** 28% **Group 2:** 21% **p value:** p < 0.001 (ANCOVA) favouring latanoprost	
			Mean ± SD IOP at 10 am and 5 pm at 6 months (mm Hg)	**<u>IOP 10 am:</u>** **Group1:** 18.1 ± 2.9 **Group 2:** 19.5 ± 3.2 p < 0.001 (ANCOVA) in favour of latanoprost **<u>IOP 5 pm:</u>** **Group 1 :** 17.8 ± 3.0 **Group 2:** 19.8 ± 3.4 **p value:** p < 0.001 (ANCOVA) in favour of latanoprost	
			Number of patients with systemic adverse events*	**Group1:** 23 (including 4 respiratory) **Group 2:** 56 (including 4 respiratory, 1 serious) **p value:** p < 0.005 Fisher exact test (this is for all systemic side effects as defined in the paper). **95% CI:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 187 **Age (mean):** 64 ± 11 **M/F:** 77/110 **Mean IOP:** 25.1 ± 3.7 This group had significantly (p=0.027) more OHT patients than group 2. **Drop outs:** 5 (including IOP not controlled, ocular irritation, Argon laser trabeculoplasty and corneal oedema) **Group 2** **N:** 192 **Age (mean):** 65 ± 12 **M/F:** 77/115 **Mean IOP:** 24.9 ± 3.0 **Drop outs:** 47 (including 4 before instillation of treatment. Other reasons for withdrawing included 14 ocular allergic reactions, 13 IOP not controlled, withdrawal of consent and Argon laser trabeculoplasty).	mean of the 2 eyes was used.	**Number of patients with ocular adverse events****	**Group1:** 62 **Group 2:** 95 **p value:** NS except for significantly more ocular allergic reactions (p < 0.001 Fisher exact test) in the brimonidine group. **95% CI:** NR	patients randomised to receive brimonidine who withdrew consent. *includes respiratory, dry mouth, headaches, fatigue and infection **includes ocular irritation, ocular allergic reaction, increased iris pigmentation, disturbed vision and conjunctival disorders

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 8 Carbonic anhydrase inhibitors vs. no treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Miglior et al., 2005[99] European Glaucoma Prevention Study (EGPS) Group. **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** Median 55.3 months.	**Patient group:** Consecutive patients from clinic population with ocular hypertension (30 years plus). **Setting:** Patients from 18 centres in 4 European countries. **Inclusion:** IOP (22-29mmHg), two normal and reliable visual fields and normal optic discs, PEX allowed (below 2%), normal optic discs in both eyes, open angle, PEX and PDS allowed. **Exclusion**: Visual acuity below 20/40, previous intraocular surgery, previous laser trabeculoplasty within 3 months, secondary causes of elevated IOP. **<u>All patients</u>** **N:** 1077 **Age (mean):** 57.03 ± 10.3 **Race:** Caucasian: 1075, African European: 1 Asian: 1 **Mean IOP**: 23.6 ± 1.6 **<u>Group 1</u>** **N:** 536 **Age (mean):** 56.42 ± 10.32 **M/F:** 232/304 **Mean IOP**: 23.4 ± 1.53 **Dropouts**: 191 (116 adverse events) **<u>Group 2</u>** **N:** 541 **Age (mean):** 57.63 ± 10.30 **M/F:** 259/282	**Group 1** Dorzolamide 2% (CAI) – three times daily. **Group 2** Placebo – three times daily.	**Development of reproducible visual field defects:**	**Group1:** 26/536 (4.9%) **Group 2:** 38/541 (7.0%) **OR:** 0.68 (95% CI: 0.41-1.12)	**Funding:** Supported by The European Commission (BIOMED II program, contract no.: BMH4-CT-96-1598), and Merck (Whitehouse Station, NJ). **Limitations:** High dropouts (30.1%). A comparative analysis of the mean IOP between patients still in the study and those who voluntarily withdrew revealed a higher IOP level in the group of withdrawn patients. It was not possible to calculate standard deviations for mean change in IOP from baseline at each follow up using Cochrane methods because no p values were reported.. **Additional outcomes:** **Notes:** Randomisation by computer generated allocation sequence and allocation concealment. Patients and examiners were masked to treatment assignment. Initially 1081 enrolled and
			Dropouts due to adverse events:	**Group1:** 116/536 (21.7%) **Group 2:** 51/541 (9.4%) **OR:** 2.54 (95% CI: 1.83-3.53)	
			Development of reproducible VF defect or glaucomatous change of optic disc:	**Group1:** 46/536 **Group 2:** 60/541 **OR:** 0.86 (95% CI: 0.58-1.26) **p value:** 0.45	
			Mean IOP at follow up	**<u>6 months</u>** **Group 1:** 20 ± 2.69 (n=484) **Group 2:** 21.3 ± 2.98 (n=492) **<u>12 months</u>** **Group 1:** 19.7 ± 2.88 (n=453) **Group 2:** 21 ± 3.41 (n=475) **<u>2 years</u>** **Group 1:** 19.1 ± 2.85 (n=391) **Group 2:** 20.4 ± 3.35 (n=447) **<u>5 years</u>** **Group 1:** 18.2 ± 3.45 (n=192) **Group 2:** 19.1 ± 3.71 (n=217)	
			Mean % reduction from baseline in observed cases:	**6Months** **Group1:** 14.5% **Group 2:** 9.3% **5 years:** **Group 1:** 22.1% **Group 2:** 18.7%	
			Mean % reduction IOP from baseline in last	**Group1:** 17.9% (SD 14.1%) **Group 2:** 13.7% (SD 15.9%)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Mean IOP: 23.5 ± 1.68 **Drop outs**: 134 (51 adverse events)		**observation carried forward analysis:** (5 years)		randomised but 4 excluded as had glaucoma so not included in intention to treat analysis.
			Safety endpoint (IOP 35mmHg or greater):	**Group 1:** 1/536 (0.2%) **Group 2**: 12/541 (2.2%)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 9 Carbonic anhydrase inhibitors vs. beta-blockers

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
March & Ochsner, 2000[92] The Brinzolamide Long-Term Therapy Study Group **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 18 months	**Patient group:** COAG or OHT **Setting:** multi-centre (18 sites) USA **Inclusion criteria:** • Diagnosis of pseudoexfoliative glaucoma, POAG, pigmentary glaucoma or OHT • ≥21 years old • Post menopausal or sterilised women only • IOP 22 – 36 mmHg after washout period **Exclusion criteria:** • Patients with corrected visual acuity of worse than 20/80 • Pregnant or nursing women • Patients with history of hypersensitivity to test medications • Previous intraocular surgery • Ocular trauma • Recent ocular inflammation or infection • Photophobia or diplopia • Contraindications to beta-blockers, CAI • Use of medications causing dry eye • Concomitant use of systemic CAIs **<u>All patients</u>** **N:** 378	**Group 1** Brinzolamide 1% 2/day (+ placebo for afternoon dose) **Group 2** Brinzolamide 1% 3/day **Group 3** Timolol 0.5% 2/day (+ placebo for afternoon dose) **Examination Methods:** At each visit the IOP was measured before the morning dose using a Goldmann tonometer. Automated perimetry was performed at month 12 and on completion.	**Mean ± SD baseline IOP mmHg** (average of both eyes 8am)	**Group1:** 25.1 ± NR **Group 2:** 26.1 ± NR **Group 3:** 25.4 ± NR	**Funding:** Alcon laboratories. Manufacturer of brinzolamide **Limitations:** • Randomisation method and allocation concealment not reported. • Although study states that it is a double masked design it is not clear whether examiners are masked • SDs missing from IOP outcome data • High dropout rate. • Results presented are per protocol not ITT **Additional outcomes:** Corneal thickness and corneal endothelial cell density **Notes:** Randomisation 2:2:1 Drop out figures due to
			Mean ± SD reduction in IOP mmHg at 18 mths (baseline – end point)	**Group1:** 3.3 ± NR **Group 2:** 3.2 ± NR **Group 3:** 5.3 ± NR P is < 0.002 comparing timolol v brinzolamide 2/day or 3/day	
			Number of patients reporting local ocular side effects	**Group1:** 45 **Group 2:** 47 **Group 3:** 19 Includes itching, stinging, vision disturbance, eyelid discomfort, hyperaemia	
			Number of patients reporting bitter taste	**Group1:** 5 **Group 2:** 12 **Group 3:** 0	
			Number of patients with cardiovascular systemic side effects	**Group1:** NR **Group 2:** NR **Group 3:** NR	
			Reasons for withdrawals (dropouts)	**Group1:** • Inadequate IOP control = 9 • Adverse events = 21 • Other (includes self-withdrawal, lost to follow-up, non-compliance) = 14 **Group 2:** • Inadequate IOP control = 13 • Adverse events = 17 • Other (includes self-withdrawal, lost to follow-up, non-compliance) = 33 **Group 3:** • Inadequate IOP control = 1 • Adverse events = 8	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 150 **Age (mean ± SD):** 63.0 ± 11.6 **M/F:** 68/82 **Black/non-black:** 27/123 **OHT/COAG:** 59/91 **Drop outs:** 44 (29%) **Group 2** **N:** 153 **Age (mean ± SD):** 60.3 ± 12.9 **M/F:** 76/77 **Black/non-black:** 33/120 **OHT/COAG:** 57/96 **Drop outs:** 63 (41%) **Group 3** **N:** 75 **Age (mean ± SD):** 59.9 ± 13.2 **M/F:** 28/47 **Black/non-black:** 14/61 **OHT/COAG:** 25/50 **Drop outs:** 27 (36%)			• Other (includes self-withdrawal, lost to follow-up, non-compliance) = 18	other reasons include proportion of patients withdrawing from study at 12 months. Patients are masked to treatment assignment

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Carbonic anhydrase inhibitors vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Strahlman et al., 1995[145] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** COAG & OHT **Setting:** multi-centre, 34 sites **Inclusion criteria:** • 21 – 85 years old • Sufficient washout period for current medications • Untreated IOP of ≥ 23 mmHg • Contact lens wearing discontinued 3 weeks prior to study **Exclusion criteria:** • Patients whom discontinuation of current treatment would cause glaucomatous damage • Patients with corrected visual acuity of worse than 20/60 • History of poor response to ocular hypotensive agents • History of allergy to agents in trial • Contraindications to beta-blockers • Clinically significant dry eye syndrome • Previous intraocular surgery • Ocular trauma • Recent ocular inflammation or infection • Herpes simplex keratitis or corneal ulcer within 1 year • Photophobia or diplopia • Premenopausal, pregnant and nursing women • Concomitant use of systemic	**Group 1** Dorzolamide 2% 3/day **Group 2** Timolol 0.5% 2/day (+ placebo for afternoon dose) **Group 3** Betaxolol 0.5% 2/day (+ placebo for afternoon dose) **Examination methods:** Within each centre investigators were instructed to use the same Goldman tonometer for all IOP measurements for a given patient. IOP was measured at weeks 2, 4 and months 2,3,6,9 and 12. IOP measured at 9.30am, 12.30pm and 3.30pm Humphrey 24-2 or Octopus perimetry was used for the visual field testing at screening and months 6 and 12	**Mean ± SD baseline IOP mmHg** reading at 12.30 pm	**Group1:** 25.2 ± 4.8 **Group 2:** 25.9 ± 5.3 **Group 3:** 26.1 ± 5.7	**Funding:** Merck & co inc. Manufacturers of dorzolamide and timolol **Limitations:** • Randomisation method and allocation concealment not reported. • Although study states that it is a double masked design it is not clear whether examiners are masked • Some patients received additional therapy (timolol or dorzolamide) if IOP was not lowered effectively on monotherapy. The dropout numbers include all patients. **Additional outcomes:** **Notes:** 3:1:1 randomisation Patients are masked to treatment assignment.
			Mean ± SD end point IOP reading at 12.30 pm **12 mths**	**Group1:** 20.5 ± 5.0 **Group 2:** 19.9 ± 4.0 **Group 3:** 20.9 ± 5.4	
			Mean ± SD reduction in IOP mmHg at 12 mths (baseline – end point) reading at 12.30 pm	**Group1:** 4.7± 4.1 **Group 2:** 6.0 ± 4.2 **Group 3:** 5.2 ± 4.9	
			Number of patients reporting local ocular side effects	**Group1:** 195 **Group 2:** 44 **Group 3:** 47 Includes itching, stinging, vision disturbance, eyelid discomfort, conjunctivitis	
			Number of patients reporting bitter taste	**Group1:** 85 **Group 2:** 7 **Group 3:** 9	
			Number of patients with cardiovascular systemic side effects	**Group1:** 8 **Group 2:** 8 **Group 3:** 9 Includes hypertension, angina, tachycardia	
			Reasons for withdrawals (dropouts)	**Group1:** • Inadequate IOP control = 10 • Adverse events = 37 • Administration = 14 **Group 2:** • Inadequate IOP control = 1 • Adverse events = 6 • Administration = 6 **Group 3:** • Inadequate IOP control = 6	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	beta-blockers or CAIs which may affect IOP **<u>All patients</u>** **N:** 523 **Age (mean):** 64 (range 17-85) **M/F:** 243/280 **Drop outs:** 89 **<u>Group 1</u>** **N:** 313 **Age (mean ± SD):** 62.1 ± 11.6 **M/F:** 136/177 **Black/non-black:** 4/309 **OHT/COAG:** 120/220* **Drop outs:** 61 **<u>Group 2</u>** **N:** 103 **Age (mean ± SD):** 63.8 ± 11.4 **M/F:** 53/50 **Black/non-black:** 2/101 **OHT/COAG:** 44/68* **Drop outs:** 13 **<u>Group 3</u>** **N:** 107 **Age (mean ± SD):** 60.7 ± 12.0 **M/F:** 54/53 **Black/non-black:** 3/104 **OHT/COAG:** 33/83* **Drop outs:** 15 * based on eye rather than patient			• Adverse events = 3 • Administration = 6	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 10 Sympathomimetics vs. beta-blockers

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Le Blanc, 1998[83] and Schuman, 1996[132] **$** **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG & OHT **Setting:** multi-centre, Canada & USA **Inclusion criteria:** • Diagnosis of POAG or OHT and on no more than 2 glaucoma drugs • Best corrected visual acuity of 20/80 or better in each eye • Untreated IOP between 23 and 35 mmHg and both eyes within 5 mmHg each other • Washout of current medications **Exclusion criteria:** • Active ocular disease • Severe dry eye • Corneal abnormalities • Advanced glaucoma (C/D≥ 0.8) • Contact lens wearers • Use of other ocular medications • Surgery or laser surgery within 6 months • Uncontrolled hypertension or diabetes • Women with child bearing potential • Contraindications to	**Group 1** Brimonidine 0.2% 2/day **Group 2** Timolol 0.5% 2/day **Examination methods:** IOP was measured at trough - 12 hours after instillation of evening medication and at peak - 2 hours after morning medication. Study does not report how IOP was measured. Horizontal cup to disc ratios and visual field measured using a Humphrey perimeter (Mean Deviation) at months 6 and 12. Snellen chart used for visual acuity at each visit. Direct and indirect ophthalmoscopy was used to evaluate the fundus and optic nerve head. Schirmer tear test at 6 and 12 months	**Mean & 95% CI reduction in peak IOP mmHg (averaged over all time points to 12 months)**	**Group1:** 6.8 CI (7.2 - 6.4) **Group 2:** 5.9 CI (6.4 - 5.4) Group1 was significantly better at reducing pressure than group2 p value < 0.001 at weeks 1 & 2 and month 12 using paired t-test	**Funding:** Allergan Inc. Manufacturers of Brimonidine **Limitations:** Very high drop out rate for brimonidine group 47% **Additional outcomes:** Mean Heart Rate **Notes:** Randomisation by computer generated allocation sequence and allocation concealment. Patients and examiners were masked to treatment assignment. Uneven randomisation. **3:2** **$** Schuman 1996[132] reports intermediate results of Le Blanc 1998[83] (6 months of data) and Schuman 1997 *Drop out figures include those who were
			Mean & 95% CI reduction in trough IOP mmHg (averaged over all time points to 12 months)	**Group1:** 3.9 CI (4.2 - 3.6) **Group 2:** 6.0 CI (6.4 - 5.6) Group2 was significantly better at reducing pressure than group1 p value < 0.001 at all time points using paired t-test	
			Mean ± SD reduction in diurnal IOP mmHg (averaged over all time points to 12 months)	**Group1:** 5.4 ± NR **Group 2:** 5.9 ± NR	
			Mean ± SD baseline peak IOP mmHg 6 months Data from Schuman1996	**Group1:** 25.06 ± 3.38 **Group 2:** 24.73 ± 3.12	
			Mean ± SD reduction in peak IOP mmHg (baseline – end point) 6 months Data from Schuman1996	**Group1:** 6.44 ± 3.86 **Group 2:** 5.8 ± 3.66	
			Mean ± SD baseline trough IOP mmHg 6 months Data from Schuman1996	**Group1:** 25.96 ± 3.01 **Group 2:** 25.85 ± 2.8	
			Mean ± SD reduction in trough IOP mmHg	**Group1:** 3.79 ± 3.37 **Group 2:** 6.10 ± 3.12	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	betablockers or α adrenergic agonists • Hypersensitivity to treatment medications • Those who have participated in previous trial within 30 days start of study. **<u>All patients</u>** **N:** 463 **Age (mean):** NR **M/F:** 234/229 **<u>Group 1</u>** **N:** 280 **Age (mean):** 63 (28.5 - 86.4) **M/F:** 138/142 **Drop outs:** 137/292* **POAG:** 157 **OHT:** 112 **1 eye OHT/1 eye POAG:** 11 **Black:** 32 **Non-black:** 260 **Dropouts:** 137/292* (47%) **<u>Group 2</u>** **N:** 183 **Age (mean):** 61 (32.8 - 83) **M/F:** 96/87 **Drop outs:** 40/191* **POAG:** 98 **OHT:** 78 **1 eye OHT/1 eye POAG:** 7 **Black:** 15 **Non-black:** 168 **Dropouts:** 40/191 (21%)*		**(baseline – end point) 6 months** Data from Schuman1996		eligible for study but didn't begin protocol.
			Possible worsening of visual field (increase >5dB for Mean Deviation)	**Group1:** 5 **Group 2:** 6 No significant between group differences in VF observed	
			***Reasons for withdrawals (dropouts)**	**Group1:** • Inadequate IOP control = 30 • All adverse events = 76 • Ocular Adverse events =43 • Systemic =16 (includes fatigue or drowsiness, headache, dry mouth) • Other reasons (including cataract surgery = 31 **Group 2:** • Inadequate IOP control = 10 • All adverse events = 9 (3 for fatigue or drowsiness) • Other reasons (including cataract surgery = 21	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Sympathomimetics vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Schuman, 1997[133] and Schuman, 1996[132] **$** **Study design:** RCT **Evidence level:** 1+ Double masked **Duration of follow-up:** 12 months	**Patient group:** POAG & OHT **Setting:** multi-centre, USA **Inclusion criteria:** • Diagnosis of POAG or OHT and on no more than 2 glaucoma drugs • Best corrected visual acuity of 20/80 or better in each eye • Untreated IOP between 23 and 35 mmHg and both eyes within 5 mmHg each other **Exclusion criteria:** • Active ocular disease • Severe dry eye • Corneal abnormalities • Advanced glaucoma (C/D≥ 0.8) • Contact lens wearers • Use of other ocular medications • Surgery or laser surgery within 6 months • Uncontrolled hypertension or diabetes • Women with child bearing potential • Contraindications to beta-blockers or α adrenergic agonists • Hypersensitivity to treatment medications • Those who have participated in	**Group 1** Brimonidine 0.2% 2/day **Group 2** Timolol 0.5% 2/day **Examination methods:** IOP was measured at trough - 12 hours after instillation of evening medication and at peak - 2 hours after morning medication. Study does not report how IOP was measured. Horizontal cup to disc ratios and visual field measured using a Humphrey perimeter (Mean Deviation) at months 6 and 12. Snellen chart used for visual acuity at each visit. Direct and indirect ophthalmoscopy was used to evaluate the fundus and optic nerve head. Schirmer tear test at 6 and 12 months	**Mean ± SD reduction in peak IOP mmHg (averaged over all time points to 12 months)**	**Group1:** 6.5 ± NR **Group 2:** 6.1 ± NR No significant difference between groups	**Funding:** Allergan Inc. Manufacturers of Brimonidine **Limitations:** • Study says it is double blind randomised trial (1:1) but the randomisation method is not stated. • No mention of evaluators being masked in methods. • Study reports that patients are given medication in a masked fashion but no further details are available • *Dropout rates were reported as % some as <1.0% so difficult to calculate numbers. Also reported for all those randomised to study including who received treatment but who didn't meet protocol entry criteria. • In the context of adverse events the study was biased towards timolol as most patients had already been taking timolol and therefore tolerated the treatment much better than brimonidine. **Additional outcomes:** Schirmer tear test - significant
			Mean ± SD reduction in trough IOP mmHg (averaged over all time points to 12 months)	**Group1:** 4.3 ± NR **Group 2:** 6.3 ± NR P is significant	
			Mean ± SD baseline peak IOP mmHg 12 months Data from Schuman1996	**Group1:** 24.75 ± 2.97 **Group 2:** 24.56 ± 3.04	
			Mean ± SD reduction in peak IOP mmHg (baseline – end point) 12 months Data from Schuman1996	**Group1:** 5.92 ± 3.19 **Group 2:** 6.01 ± 3.35	
			Mean ± SD baseline trough IOP mmHg 12 months Data from Schuman1996	**Group1:** 25.80 ± 2.31 **Group 2:** 25.87 ± 2.81	
			Mean ± SD reduction in trough IOP mmHg (baseline – end point) 12 months Data from Schuman1996	**Group1:** 3.67 ± 3.98 **Group 2:** 5.88 ± 3.38	
			Possible worsening of visual field (subset of patients)	**Group1:** 17/77 (22.1%) **Group 2:** 23/111 (20.7%)	
			Number of patients	**Group1:** 325	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	previous trial within 30 days start of study. **<u>All patients</u>** **N:** 374 **Age (mean ± SD):** 63 ± 11 **M/F:** 50:50 **Drop outs:** NR* **<u>Group 1</u>** **N:** 186 **Age (mean):** NR **M/F:** NR **Drop outs:** 35 **<u>Group 2</u>** **N:** 188 **Age (mean):** NR **M/F:** NR **Drop outs:** 4		**reporting local ocular adverse events**	**Group 2:** 238 Including stinging, blurring and allergic reactions, hyperaemia, photophobia, pruritis	changes from baseline for both groupd but no significant differences between groups Cup/Disc ratio – no significant changes from baseline or between group **Notes:** **$** Schuman 1996[132] reports intermediate results of Le Blanc 1998[83] (6 months of data) and Schuman 1997
			Number of patients reporting systemic adverse events	**Group1:** 159 **Group 2:** 125 Includes dry mouth, fatigue/drowsiness and headache	
			***Reasons for withdrawals (dropouts)** Data taken from Vass 2007[155] systematic review which reports drop out rates for study	**Group1:** • Local adverse events = 25 • Systemic adverse events = 10 **Group 2:** • Local adverse events = 2 • Systemic adverse events = 2	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Sympathomimetics vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Tsai, 2005[152] **Study design:** RCT **Evidence level:** 1 + **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** single centre, China **Inclusion criteria:** • Diagnosis of bilateral POAG • Best corrected visual acuity of 20/50 or better in each eye • Untreated IOP between 22 and 30 mmHg in each eye • >35 years old **Exclusion criteria:** • History of previous glaucoma drugs in previous 4 weeks • Previous laser or surgical treatments • Co-existing retinal disease or non-glaucomatous optic neuropathy • Corneal abnormalities • Lens opacity worse than NC3/NO3 • VF loss > 20dB • Diabetes mellitus • Pregnancy or childbearing potential • Contraindications or hypersensitivity to either of the drugs in trial **<u>All patients</u>** **N:** 44 **Age (mean):** NR **M/F:** NR	**Group 1** Brimonidine 0.2% 2/day **Group 2** Timolol 0.5% Gel (Timoptic) 1/day 8am **Examination methods:** IOP measured using Perkins applanation tonometry every 2 months. At 12 months VF examined using Humphrey perimetry. RNFL thickness measured using scanning laser polarimetry	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 24.2 ± 1.3 **Group 2:** 23.9 ± 1.1	**Funding:** Conducted at Chang Gung Memorial Hospital, Taiwan, Republic of China **Limitations:** Open label and examiners not masked. change in IOP and visual field progression were not primary outcomes **Additional outcomes:** RNFL thickness significantly decreased from baseline for timolol compared to brimonidine **Notes:**
			Mean ± SD end point diurnal IOP (12 mths) mmHg	**Group1:** 18.6 ± 0.9 **Group 2:** 18.7 ± 1.1	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths (baseline – end point)	**Group1:** 5.6 ± 0.8 **Group 2:** 5.3 ± 0.5 **p value:** between group using ANOVA for repeated measures = 0.16	
			Number of patients with local ocular side effects	**Group1:** NR **Group 2:** NR	
			Number of patients with cardiovascular systemic side effects	**Group1:** NR **Group 2:** NR	
			Reasons for withdrawals (dropouts)	**Group1:** • Inadequate IOP control = 2 • Allergic blepharoconjunctivitis = 1 **Group 2:** • Inadequate IOP control = 2	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 5 **<u>Group 1</u>** **N:** 22 **Age (mean):** 61.9 ± 8.6 **M/F:** NR **Drop outs:** 3 **<u>Group 2</u>** **N:** 22 **Age (mean):** 60.0 ± 9.4 **M/F:** NR **Drop outs:** 2				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 11 Miotics vs. beta-blockers

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Drance, 1998[36] **Study design:** RCT Single masked **Evidence level:** 1 + **Duration of follow-up:** 24 months	**Patient group:** COAG (early glaucoma including pseudoexfoliative and pigmentary glaucomas) **Setting:** single centre, Canada **Inclusion criteria:** • IOP ≥ 24 mmHg • Disc and field abnormality • Field abnormality include localised scotomata but not to preclude reliable follow up <10 dB • Previous glaucoma therapy discontinued 4 weeks prior to start of study **Exclusion criteria:** • Previous ocular trauma, uveitis, inflammatory disease or infections • Previous laser or surgical treatments within 3 or 6 months respectively • History of retinal disease • Current contact lens wearers • Premenopausal women not on birth control • Severe or unstable cardiovascular or pulmonary disease • Chronic renal failure • Cerebrovascular disease • Systemic use of glucocorticoids and other medications affecting IOP • Contraindications or hypersensitivity to either of the drugs in trial **<u>All patients</u>** **N:** 68 **Age (mean):** 63 **M/F:** NR **Drop outs:**	**Group 1** Betaxolol 0.5% 2/day **Group 2** Timolol 0.5% 2/day **Group 3** Pilocarpine 2% 4/day **Examination methods:** Follow up at 3,6,12,18,24 months and all patients visual fields tests on Octopus perimeter or 30-2 Humphrey blue/yellow, Snellen acuity, tonometry, blood pressure, pulse and optic disc evaluation	**Incidence of visual field progression defined as Least-squares mean defect (dB change from baseline)**	**Group 1:** 0.98 dB **Group 2:** 0.87 dB **Group 3:** 0.83 dB **T v P =** 0.95 **not signif.** **B v P =** 0.85 **not signif.**	**Funding:** Alcon laboratories **Limitations:** • Randomisation method and allocation concealment were not reported • Timolol and betaxolol masked. Pilocarpine open label • Adverse events not reported in details **Additional outcomes:** **Notes:**
			IOP at baseline mmHg	**Group 1:** 24.1 ± 3.8 **Group 2:** 23.9 ± 2.3 **Group 3:** 25.1 ± 4.1	
			Change in IOP from baseline *Estimated from line graph at 24 months*	**Group 1:** 4.1 ± NR **Group 2:** 4.5 ± NR **Group 3:** 4.8 ± NR **Not signif.**	
			Reasons for drop out:	**Group 1: 3** inadequate IOP control = 2 adverse event = 1 **Group 2: 7** inadequate IOP control = 2 patient decision = 2 other = 3 **Group 3: 3** Unacceptable local side effects = 3	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 27 **Age (mean):** 65.3 ± 12.5 **Baseline IOP ± SD mmHg:** 24.1 ± 3.8 **M/F:** 52/48 (%) **Mean MD (dB):** 5.2 ± 4.6 **Race:** White: 100% **Drop outs:** 3 **Group 2** **N:** 27 **Age (mean):** 59.6 ± 15.8 **Baseline IOP ± SD mmHg:** 23.9 ± 2.3 **M/F:** 67/33 (%) **Mean MD (dB):** 4.5 ± 2.3 **Race:** White: 89% **Drop outs:** 7 **Group 3** **N:** 14 **Age (mean):** 64.1 ± 7.7 **Baseline IOP ± SD mmHg:** 25.1 ± 4.1 **M/F:** 57/43 (%) **Mean MD (dB):** 3.9 ± 2.8 **Race:** White: 86% **Drop outs:** 3				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Miotics vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Sponsel, 1987[141] & Dallas et al., 1988[29] **Study design:** RCT **Evidence level:** 1 + **Duration of follow-up:** 17 months - 2 years	**Patient group:** COAG **Setting:** single centre, UK **Inclusion criteria:** • IOP ≥ 21 mmHg on 2 occasions • Optic disc cupping supportive of glaucoma • Visual field loss typical of nerve fibre bundle damage **Exclusion criteria:** • Co-existing pathology • Substantive acuity deficit 6/9 or worse • Retinal problems likely to affect plotting • Contraindications to Timolol **<u>All patients</u>** **N:** 50* **Age (mean):** NR **M/F:** 60/40 (%) **Drop outs:** 14* **<u>Group 1</u>** **N:** 25 **Age (mean):** 62.5 ± NR **Baseline IOP ± SD mmHg**: 28.0 ± 6.3 **M/F:** NR **Drop outs:** 3 **<u>Group 2</u>** **N:** 25 **Age (mean):** 68.7 ± NR **Baseline IOP ± SD mmHg**: 27.6 ± 4.7 **M/F:** NR **Drop outs:** 11	**Group 1** Timolol 0.5% or 0.25% 2/day **Group 2** Pilocarpine 2% or 4% 2/day **Examination methods:** Patients followed every 3 months and visual field measured using Goldmann and Friedmann static suprathreshold perimetry and IOP measured using Goldmann tonometry	**Rate of VF loss in units/month. Friedmann analysis**	**Group 1:** 0.46 **Group 2:** 0.92 **Signif.**	**Funding:** Alcon laboratories **Limitations:** • Randomisation method and allocation concealment not reported. • Open label study • Masking of examiners is not reported • Adverse events not reported **Additional outcomes:** **Notes:** *Original randomised patients reported in the other paper Dallas et al., 1998[29] but dropouts were not clearly reported. Could be due to miotic intolerance but figures do not add up.
			IOP at baseline mmHg	**Group 1:** 28.0 ± 6.3 (n=22) **Group 2:** 27.6 ± 4.7 (n=14)	
			IOP at end point mmHg (Averaged 6 measurements over 24 month follow up)	**Group 1:** 21.2 ± 5.1 (n=22) **Group 2:** 20.9 ± 1.9 (n=14)	
			Change in IOP from baseline at end point	**Group 1:** 6.8 ± NR (n=22) **Group 2:** 6.7 ± NR (n=14)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Miotics vs. beta-blockers (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Vogel et al., 1992[157] **Study design:** RCT Single masked **Evidence level:** 1 + **Duration of follow-up:** 2 years	**Patient group:** POAG **Setting:** multi-centre, international – USA, UK & Canada] **Inclusion criteria:** • IOP ≥ 22 mmHg on at least 1/5 measurements taken over 1 day after washout period of 7 days • Open angles • Visual field defect of ≥ 3 test points > 5 dB recorded by Octopus 30 programme • Optic disc cupping supportive of glaucoma • Visual field loss typical of nerve fibre bundle damage **Exclusion criteria:** • History of ocular trauma or intraocular surgery • Corneal ulcer, ocular infection or herpatic keratitis 3 months prior to study • Closed angle or secondary glaucoma • Bronchial asthma or COPD • >first degree heart block • Uncompensated heart failure • Bradycardia • Concomitant medications affecting IOP • Pregnant or nursing women • Contraindications to Timolol **<u>All patients</u>** **N:** 189 **Age (mean):** NR **M/F:** NR	**Group 1** Timolol 0.5% or 0.25% 2/day **Group 2** Pilocarpine 2% or 4% 2/day **Examination methods:** After washout period measurements of VF, IOP, slit lamp examination, gonioscopy, ophthalmoscopy, visual acuity. VF measured every 4 months on Octopus 30 programme. Patients withdrawn if IOP > 25 mmHg or VF worsened rapidly. Worse eye was used for efficiacy analysis or if both eyes the same the right eye was used.	**Difference in mean VF score dB at 24 months**	**Group 1:** + 0.5 dB **Group 2:** - 1.2 dB P < 0.01 **Signif.**	**Funding:** Alcon laboratories **Limitations:** • High drop out rate. Data on VF (51 patients) and IOP (91 patients) not collected at baseline • Randomisation method and allocation concealment not reported. • Baseline demographic data not reported • Open label study but observer masked • Adverse events not reported **Additional outcomes:** **Notes:** *Not clear from study what patients did not start study or reasons for dropout. IOP data at baseline only available for 98 patients. Visual field data only available at baseline for 138
			Mena visual field threshold at baseline dB	**Group 1:** 18.5 ± 6.2 (n=75) **Group 2:** 16.9 ± 5.7 (n=63)	
			Mean number of Test Points showing deterioration at 24 months	**≥5 dB** **Group 1:** 4.5 ± 5.3 (n=46) **Group 2:** 13.5 ± 13.6 (n=26) P <0.01 **≥7 dB** **Group 1:** 2.3 ± 3.2 (n=46) **Group 2:** 6.7 ± 9.4 (n=26) P <0.01 **≥10 dB** **Group 1:** 1.1 ± 1.7 (n=46) **Group 2:** 3.5 ± 5.7 (n=26) P <0.01	
			IOP at baseline mmHg	**Group 1:** 26.9 ± 3.6 (n=53) **Group 2:** 27.9 ± 5.1 (n=45)	
			IOP at 24 months mmHg	**Group 1:** 20.8 ± 2.6 (n=36) **Group 2:** 21.9 ± 2.7 (n=20) **Not signif.**	
			Change in IOP from baseline at end point	**Group 1:** 6.8 ± NR (n=36) **Group 2:** 6.7 ± NR (n=20)	
			Discontinuation due to lack of IOP control	**Group 1:** 14% **Group 2:** 35%	
			Discontinuations for other reasons	**Group 1: 16** Taking concomitant beta-blocker = 1 Lost to follow up = 5 Patient uncooperative = 1 Protocol deviation = 2 Study ended before 24 mths	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: * **<u>Group 1</u>** **N:** * **Age (mean):** NR **Baseline IOP ± SD mmHg:** **M/F:** NR **Drop outs:** * **<u>Group 2</u>** **N:** * **Age (mean):** NR **Baseline IOP ± SD mmHg: M/F:** NR **Drop outs:** *			completed = 6 VF unsatisfactory = 1 **Group 2: 19** Taking concomitant beta-blocker = 1 Developed exclusion criteria = 1 Developed angle closure = 1 Lost to follow up = 7 Protocol deviation = 4 Study ended before 24 mths completed = 4 VF unsatisfactory = 1	patients.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 12 Fixed combination vs. single medications

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Higginbotham et al., 2002[61] **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months (double masked RCT part of study) Study continued for a further 6 months as an open-label study with everyone receiving the fixed combination treatment.	**Patient group:** COAG or OHT **Setting:** multi-centre (38 eye clinics) USA **Inclusion criteria:** • Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Aged 18 or older • Best corrected visual acuity measuring 20/200 • Pre-study IOP ≥30mmHg without IOP reducing medication OR ≥25mmHg with prior treatment • Previous latanoprost or timolol therapy permitted **Exclusion criteria:** • History of acute angle-closure or occludable angles • Use of contact lenses • Ocular surgery, argon laser trabeculoplasty or ocular inflammation or infection within 3 months of the pre-study visit • Hypersensitivity to benzalkonium chloride • Any other abnormal ocular condition or symptom that investigator determined precluded study enrolment • Presence of concomitant diseases	**Group 1** Fixed combination of Latanoprost 0.005% & timolol 0.5% 8am AND placebo 8pm **Group 2** Latanoprost 0.005% 8am AND placebo 8pm **Group 3** Timolol 0.5% 8am AND 8pm **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer. Each measurement taken in triplicate in each eye. Measurements taken at 8am, 10am and 4pm at baseline and weeks 2, 13, 26 and 52. Automated visual field examination performed at	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 23.1 ± 3.8 **Group 2:** 22.9 ± 4.1 **Group 3:** 23.7 ± 4.1	**Funding:** Pharmacia & Upjohn Inc.; Research to Prevent Blindness Inc. **Limitations:** Run in period 2 – 4 weeks with timolol 0.5 % 2/day prior to starting study Adverse events reported by area of eye they occur making it difficult to assess total no. of patients with a particular event. **Notes:** *Differences estimated (least square mean difference) using a repeated measures analysis of covariance with baseline IOP as a covariate; patient, treatment, visit and centre as main factors; and treatment group-by-visit and treatment group-by-centre interaction factors. **§** values not reported for group 2 to group 3 Intention to treat analysis for the first 6 months included all patients who received at least
			Mean ± SD diurnal IOP at 6 mths mmHg	**Group1:** 19.9 ± 3.4 **Group 2:** 20.8 ± 4.6 **Group 3:** 23.4 ± 5.4	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths §	**Group1 to Group 3:** -2.9 (95% CI: -3.5 to -2.3, p<0.001)* **Group 1 to Group 2:** -1.0 (95% CI: -1.7 to -0.3, p=0.005)*	
			Mean ± SD reduction in diurnal IOP mmHg at 6 mths	**Group 1:** 3.2 ± 3.16 ** **Group 2:** 2.1 ± 4.23** **Group 3:** 0.3 ± 4.20**	
			Percent of patients reaching IOP <15mmHg at of 6 mths §	**Group1:** 6 /130 **Group 2:** 4/128 **Group 3:** 1/129 **P value (group 1 to 3):** 0.06 **P value (group 1 to 2):** 0.56	
			Percent of patients reaching IOP <18mmHg at of 6 mths § *Used in met-analysis*	**Group1:** 28/130 **Group 2:** 30/128 **Group 3:** 8/129 **P value (group 1 to 3)** =0. 01 **P value (group 1 to 2)** =0. 65	
			Percent of patients reaching IOP <21mmHg at of 6 mths §	**Group1:** 68/130 **Group 2:** 63/128 **Group 3:** 39/129 **P value (group 1 to 3)** <0.001 **P value (group 1 to 2)** =0.36	
			Number of ocular side effects †	**Group1:** 86 **Group 2:** 86 **Group 3:** 59	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	that contraindicate adrenergic antagonist • Nursing mothers, pregnant women and women who were of childbearing potential not using adequate contraception for at least the previous 3 months • Patients who could not adhere to treatment or the visit plan • Patients who had participated in another clinical study within 1 month of previous visit **<u>All patients</u>** **N:** 418 **Age (mean):** NR **M/F:** 215/203 **Drop outs:** 73 **Ethnicity:** white 276, black 110, Hispanic 27, other 5 **Diagnosis:** POAG 278, pseudoexfoliative glaucoma 9, pigmentary glaucoma 13, OHT 109, mixed (different diagnosis in the two eyes) 8, none listed 1 **IOP reducing medication in last 3 months**: 351/418 **<u>Group 1</u>** **N:** 138 **Age (mean):** 61 ±12 **M/F:** 67/71 **Drop outs:** 13 **Ethnicity:** white 90, black 38, Hispanic 7, other 3 **Diagnosis:** POAG 94, pseudoexfoliative glaucoma 2,	baseline and weeks 13, 26 and 52. Visual acuity assessed and eye-lid slit lamp biomicroscopy performed at each visit. Ophthalmoscopy performed at pre-study visit and weeks 26 and 52.		† side effects include blephartis, hypertrichosis, irritation, melbomianitis, seborrhea, eye hyperaemia, chemosis, conjunctival discolouration, corneal disorder, keratitis, keratopathy, cataract, optic atrophy, errors of refraction, increased IOP, vision decreased, visual field defect, conjunctivitis, epiphora, eye pain, photophobia, vision blurred	one drop of medication. For IOP measurements the last available IOP measurement was carried forward. ** Standard deviations (SD) for fixed v monotherapy calculated using the Cochrane method for imputed SDs from the mean correlation coefficients calculated from Ozturk 2007[115] (CAI + BB v PGA) Computer generated randomisation sequence. Patients and examiners were masked to treatment allocation
			Visual field defects	**Group1:** 7/130 **Group 3:** 4/128	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	pigmentary glaucoma 4, OHT 36, mixed 2, none listed 0 **IOP reducing medication in last 3 months**: 117/138 **<u>Group 2</u>** **N:** 140 **Age (mean):** 63 ±13 **M/F:** 80/60 **Drop outs:** 36 **Ethnicity:** white 90, black 35, Hispanic 14, other 1 **Diagnosis:** POAG 95, pseudoexfoliative glaucoma 4, pigmentary glaucoma 5, OHT 33, mixed 3, none listed 0 **IOP reducing medication in last 3 months**: 117/140 **<u>Group 3</u>** **N:** 140 **Age (mean):** 63 ±12 **M/F:** 68/72 **Drop outs:** 24 **Ethnicity:** white 96, black 37, hispanic 6, other 1 **Diagnosis:** POAG 89, exfoliative glaucoma 3, pigmentary glaucoma 4, OHT 40, mixed 3, none listed 1 **IOP reducing medication in last 3 months**: 117/140				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Fixed combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ozturk et al, 2007[115] **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG or OHT **Setting:** ophthalmology clinic, Turkey **Inclusion criteria:** • IOP ≥21mmHg without medication Washout period for topical medications prior to baseline visit (CAI – 1 week, beta-blockers – 4 weeks, prostaglandins – 6 weeks) **Exclusion criteria:** • IOP >35mmHg • History of chronic or recurrent inflammatory eye disease • Ocular trauma • Ocular infection • Severe retinal disease • Previous intraocular or laser surgery • Any condition preventing reliable applanation tonometry • Use of any systemic medication that might affect IOP • Unstable cardiopulmonary disease **<u>All patients</u>** **N:** 65 **<u>Group 1</u>** **N:** 30 **Age (mean):** 64.9 (48-78) **M/F:** 15/14 **Drop outs:** 1	**Group 1** Fixed combination of dorzolamide & timolol (Cosopt, Merck, USA) 2/day (concentrations not reported) **Group 2** Bimatoprost 0.03% 1/day **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer. Mean of 3 consecutive measurements used. Bilateral POAG or OHT patients had eye with higher IOP selected, if eyes had equal IOP then right eye was selected. Measurements for baseline and 6 month visits taken at 8am, 12pm and 4pm.	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 24.1 ± 2.1 (n=29) **Group 2:** 23.7 ± 2.0 (n=34) **P value:** 0.38	**Funding:** not reported **Limitations:** Randomisation method and allocation concealment not reported. Adverse events poorly reported. **Additional outcomes:** Also reported IOP taken at 12.00 hours at day 15, and months 1 and 3. **Notes:** Investigators assessing IOP masked to treatments. † Reported adverse events: burning/stinging, conjunctival hyperaemia, bitter taste, dry eye, eyelid eczema, breathlessness
			Mean ± SD diurnal IOP at 6 mths mmHg	**Group1:** 17.6 ± 2.9 (n=29) **Group 2:** 17.5 ± 2.3 (n=34) **P value:** 0.89	
			Mean reduction in IOP at 6 mths	**Group1:** 6.5 ± 2.3 (n=29) **Group 2:** 6.2 ± 1.8 (n=34) **P value:** 0.89	
			No. of ocular & systemic adverse events by group (some patients had more than 1 ocular events)	**Group1:** 11 **Group 2:** 28	
			No. of patients with conjunctival hyperaemia	**Group1:** 2/29 **Group 2:** 18/34 **P value:** 0.02	
			No of patients with breathlessness	**Group1:** 0/29 **Group 2:** 1/34 **P value:** 0.47	
			Total no. dropouts	**Group1:** 1/30 **Group 2:** 1/35 **P value:** 0.71	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Ethnicity: NR **Diagnosis:** POAG 22, ocular hypertension 7, **<u>Group 2</u>** **N:** 35 **Age (mean):** 61.9 (48-75) **M/F:** 13/21 **Drop outs:** 1 **Ethnicity:** NR **Diagnosis:** POAG 26, ocular hypertension 8				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Fixed combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Pfeiffer, 2002[116] European Latanoprost Fixed Combination Study Group **Study design:** RCT Double masked **Evidence level:** 1+ **Duration of follow-up:** 6 months Plus a 6 month open-label study with all patients using the fixed combination of latanoprost and timolol	**Patient group:** COAG or OHT **Setting:** multicentre - 37 centres, Germany **Inclusion criteria:** • Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma, pseudoexfoliation glaucoma or OHT • Aged 18 or older • IOP ≥25mmHg with prior therapy • IOP ≥30mmHg without prior therapy **Exclusion criteria:** • History of angle-closure glaucoma • Previous ocular surgery, argon laser trabeculoplasty or ocular inflammation or infection 3 months prior to pre-study visit • Patients with a known hypersensitivity or contraindication to any component of study drugs **<u>All patients</u>** **N:** 436 **Age (mean):** NR **M/F:** 196/240 **Drop outs:** 72 **Ethnicity:** NR **Diagnosis: :** POAG 336, pseudoexfoliative glaucoma 22, pigmentary glaucoma 8, ocular hypertension 64, mixed (different diagnosis in the two eyes) 6 **Previous IOP reducing medication**: 401 **<u>Group 1</u>**	**Group 1** Fixed combination of latanoprost 0.005% & timolol 0.5% am, placebo pm **Group 2** Latanoprost 0.005% 1/day am, placebo pm **Group 3** Timolol 0.5% 2/day **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer at pre-study visit. Method of measurement for other visits not stated. Each measurement taken three times in each eye. Measurements for each visit taken at 8am, 10am and 4pm. Also determined at each visit: best corrected visual	**Mean ± SD baseline diurnal IOP mmHg**	**Group1:** 21.6 ± 3.8 **Group 2:** 22.5 ± 4.0 **Group 3:** 22.5 ± 4.1	**Funding:** Pharmacia Inc **Limitations:** Adverse events poorly reported. Randomisation method and allocation concealment were not reported. Although patients were masked it is not clear whether examiners were masked. **Additional outcomes:** Also reported mean diurnal IOP at week 2 and 13; no. of patients switching to open-label trial on fixed combination. **Notes:** † Reported ocular adverse events: eye irritation, visual field change (suspected), hypertrichosis, hyperaemia, vision decreased, increased iris pigmentation, corneal disorder, cataract, optic atrophy, conjunctivitis, iritis, change in refraction, blepharitis. Gives number of patients for each adverse event. § Reported non-ocular adverse events: cardiovascular disorder,
			Mean ± SD diurnal IOP at 6 mths mmHg	**Group1:** 19.0 ± 3.5 **Group 2:** 20.4 ± 4.9 **Group 3:** 21.4 ± 5.4 **P values:** not reported	
			Mean ± SD reduction in diurnal IOP at 6 mths	**Group 1:** 1.7 ± 3.19** **Group 2:** 2.1 ± 3.76** **Group 3:** 1.1 ± 4.20**	
			Percent of patients reaching IOP <15mmHg at 6 mths or up to treatment failure	**Group1:** 14/140 **Group 2:** 8/147 **Group 3:** 7/149 **P values:** not significant	
			Percent of patients reaching acceptable IOP <18mmHg at 6 mths or up to treatment failure *Used in meta-analysis*	**Group1:** 54/140 **Group 2:** 48/147 **Group 3:** 37/149 **P values:** Group 1 to 3 p<0.05	
			Percent of patients reaching IOP <21mmHg at 6 mths or up to treatment failure	**Group1:** 110/140 **Group 2:** 101/147 **Group 3:** 83/149 **P values:** not significant	
			No. of ocular adverse events by group seen in ≥1% of any treatment group (NB not no. of patients) §	**Group1:** 34 **Group 2:** 41 **Group 3:** 21	
			No. of non-ocular adverse events by group seen in ≥1% of	**Group1:** 22 **Group 2:** 18 **Group 3:** 19	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 140 **Age (mean):** 64 ±13 **M/F:** 67/73 **Drop outs:** 12 **Ethnicity:** NR **Diagnosis:** POAG 106, pseudoexfoliative glaucoma 2, pigmentary glaucoma 3, ocular hypertension 27, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication**: NR **Group 2** **N:** 147 **Age (mean):** 63 ±12 **M/F:** 77/70 **Drop outs:** 28 **Ethnicity:** NR **Diagnosis:** POAG 112, pseudoexfoliative glaucoma 13, pigmentary glaucoma 4, ocular hypertension 16, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication in last**: NR **Group 3** **N:** 149 **Age (mean):** 64 ±10 **M/F:** 52/97 **Drop outs:** 32 **Ethnicity:** NR **Diagnosis:** POAG 118, pseudoexfoliative glaucoma 7, pigmentary glaucoma 1, ocular hypertension 21, mixed (different diagnosis in the two eyes) 2 **Previous IOP reducing medication in last**: NR	acuity and slit lamp examination. Refraction recorded, ophthalmoscopy performed and Colour Polaroid photographs taken at 6 months.	**any treatment group (NB not no. of patients) §**		influenza-like symptoms, metabolic disorders, respiratory disorders, cerebrovascular disorders, vertigo, sleep disorders, headache, liver/biliary disorders Patients switched medications to the fixed combination used in for group 1 if treatment failure occurred. Treatment failure defined as increased IOP ≥10% of the mean IOP from baseline and an IOP of ≥23mmHg on two examinations within 2 weeks. Study reports numbers by group. If treatment still did not work patients were withdrawn. ** Standard deviations (SD) for fixed v monotherapy calculated using the Cochrane method for imputed SDs from the mean correlation coefficients calculated from Ozturk 2007[115] (CAI + BB v PGA)
			No. of patients not completing 6 months in randomised group *	**Group1:** 12/140 **Group 2:** 28/147 **Group 3:** 32/149 **P value group 1 to 2:** =0.006 **P value group 1 to 3:** =0.001 **P value group 2 to 3:** =0.10	
			No. of patients not completing 6 months in randomised group OR in open label trial	**Group1:** 10/140 **Group 2:** 14/147 **Group 3:** 16/149 **P values:** not significant	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Fixed combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Sherwood et al, 2006[135] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** Bilateral COAG or OHT **Setting:** ophthalmology centre, USA **Inclusion criteria:** • Baseline IOP (after washout) between 24 & 34 mmHg in each eye with no more than 5 mmHg difference between eyes • Best corrected visual acuity of 20/100 • Aged 18 and over Continuation of long-term systemic therapy that could affect IOP was allowed as long as doses were constant throughout the trial **Exclusion criteria:** • Active ocular disease • Functionally significant or progressive visual field loss in the previous year • Abnormally low or high blood pressure or pulse rate • Contraindications or sensitivity to any component of the study treatments • Use of other topical medications or other therapies that might have a substantial effect on IOP • Ocular surgery in previous 3 months • Women not using 'effective means of contraception' or who were	**Group 1** Fixed combination of brimonidine 0.2% & timolol 0.5% 2/day & placebo for 3rd administration **Group 2** Brimonidine 0.2% 3/day * **Group 3** Timolol 0.5% 2/day & placebo for 3rd administration Washout periods for previous medications: CAI & parasympathometic 4 days, sympathometics 2 weeks, beta-blockers & prostaglandins 4 weeks **Examination methods:** IOP measured by calibrated Goldmann applanation tonometer. The mean of two	**Mean baseline diurnal IOP mmHg (8am, 10am, 3pm, 5pm)**	**Group1:** 24.7, 23.3, 22.1, 21.8 (n=385) **Group 2:** 24.9, 23.5, 22.5, 22.2 (n=382) **Group 3:** 25.0, 23.5, 22.5, 22.4 (n=392) **P values:** not significant	**Funding:** Allergan Inc provided funding, had a primary role in study design, management and analysis of the data, and in the preparation of the manuscript. . **Limitations:** No measurements given for IOP or IOP change throughout the study, only graphs shown. **Additional outcomes:** **Notes:** * Brimonidine 3/day used to see whether the added dose of brimonidine provided additional IOP lowering effects. † Reported adverse events: conjunctival hyperaemia, ocular stinging, eye pruritus, allergic conjunctivitis, conjunctival folliculosis, oral dryness,
			Total no. of patients with treatment related adverse events with an incidence of ≥5% in any group and a statistically significant between group difference †	**Group1:** 204/385 **Group 2:** 240/382 **Group 3:** 160/392 **P value group 1 to 2:** =0.006 **P value group 1 to 3:** <0.001 **P value group 2 to 3:** <0.001	
			Total no. of dropouts	**Group1:** 99/385 **Group 2:** 169/382 **Group 3:** 58/392 **P value group 1 to 2:** <0.001 **P value group 1 to 3:** <0.001 **P value group 2 to 3:** <0.001	
			No. of dropouts due to adverse events	**Group1:** 55/385 **Group 2:** 117/382 **Group 3:** 20/392 **P value group 1 to 2:** <0.001 **P value group 1 to 3:** <0.001 **P value group 2 to 3:** <0.001	
			'Treatment related serious' adverse events	**Group1:** 0/385 **Group 2:** 0/382 **Group 3:** 2/392 -(respiratory distress secondary to emphysema & tachycardia, sweating & nausea) **P values:** not significant	
			Mortality	**Group1:** 2/385 **Group 2:** 2/382 **Group 3:** 1/392 **P value:** not significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	pregnant or nursing **<u>All patients</u>** **N:** 1159 **Age (mean):** 62.6 (23-89) **M/F:** 518/641 **Drop outs:** 326 **Ethnicity:** white 879, African Americans 187, Hispanic 78, Asian 11, Other 4 **Diagnosis:** POAG 762, ocular hypertension 384, mixed (different diagnosis in the two eyes) 13 **No. patients requiring washout due to previous medication**: 795 **<u>Group 1</u>** **N:** 385 **Age (mean):** 62.0 ±12.2 **M/F:** 181/204 **Drop outs:** 99 **<u>Group 2</u>** **N:** 382 **Age (mean):** 63.8 ±11.8 **M/F:** 151/231 **Drop outs:** 169 **<u>Group 3</u>** **N:** 392 **Age (mean):** 62.0 ±12.3 **M/F:** 186/206 **Drop outs:** 58	consecutive measurements were used for each eye. The median of 3 measurements for each eye was used if the first 2 measurements differed by >2mmHG. Each measurement of IOP was taken four times in each eye at 8am, 10am, 3pm and 5pm. Adverse events meausured using Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART)	**Total number of dropouts**	**Group1:** 99/385 **Group 2:** 169/382 **Group 3:** 58/392 **P value group 1 to 2:** <0.001 **P value group 1 to 3:** <0.001 **P value group 2 to 3:** <0.001	conjunctival allergy/inflammation (includes any combination of conjunctival hyperaemia, eye pruritus, follicular conjunctivitis, allergic conjunctivitis, conjunctivitis, chemical conjunctivitis, conjunctival adema and blepharoconjunctivitis. Gives number of patients for each adverse event. Significantly more events with fixed combination of brimonidine-timolol than with timolol alone for conjunctival allergy/inflammation adverse events.
			Number of patients with an acceptable IOP <17.5 mmHg	**Group1:** 202/385 **Group 2:** 105/382 **Group 3:** 127/392	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 13 Separate combination vs. single medications

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bucci, 1999[13] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG **Setting:** Multi-centre centre, Italy **Inclusion criteria:** • Diagnosis of unilateral or bilateral POAG or Pseudoexfoliation glaucoma (PXF) • Uncontrolled IOP on current beta blocker therapy • Age >18 years **Exclusion criteria:** • Current therapies other than beta adrenergic agonists • Closed anterior angle glaucoma • Severe trauma • Previous ocular inflammation in last 3 months • Any condition affecting IOP measurement • Pregnant, nursing or patients considering pregnancy • **<u>All patients</u>** **N:** 99 **<u>Group 1</u>** **N:** 49 **Age (mean ± SD):** 63 ± 12 **M/F:** 21/28 **POAG:** 43 **PXF:** 6 **Drop outs:** 4	**Group 1** Latanoprost 0.005% 1/day + Timolol 0.5% 2/day **Group 2** Latanoprost 0.005% 1/day **Examination methods:** IOP measured at baseline, 2 weeks, 3 months and 6 months using a Goldmann tonometer. 3 (9am, 12 pm and 4pm) measurements were taken in each eye and mean value used in statistical analysis.	**Mean ± SD baseline diurnal IOP mmHg**	**Group 1:** NR **Group 2:** NR	**Funding:** Not reported. Conducted at Clinica Oculistica, Universita di Roma Tor Vergata **Limitations:** • Randomisation method not described. • Open label design • Masking of outcome assessment not mentioned • No washout period for latanoprost monotherapy. • Patients were selected for inadequate IOP control on various medications including timolol + clonidine and timolol + dipivefrine • **Significance testing between arms does not appear to be on an ITT basis. **Additional outcomes:** Timolol + pilocarpine study arm
			Mean ± SD end point diurnal IOP at 6 mths	**Group 1:** NR **Group 2:** NR	
			Mean ± SD reduction in IOP mmHg at 6mths (baseline – end point) SD = SE*√n	**Group 1:** 6.1 ± 2.10 **Group 2:** 5.5 ± 2.12 P between arm difference = not signif (using ANCOVA)**	
			% patients achieving an acceptable 30% reduction in IOP *<20% reduction from baseline (~21 mmHg) is approx <18 mmHg*	**Group 1:** 30/45 (not ITT) **Group 2:** 32/46 (not ITT)	
			Total number of local ocular side effects by group	**Group 1:** 21 **Group 2:** 17 Includes itching, stinging, conjunctivitis, vision disturbance and conjunctival hyperaemia	
			Total number of systemic side effects by group	**Group 1:** 1 **Group 2:** 4	
			Total number of patients with hyperaemia	**Group 1:** 8/49 **Group 2:** 4/50	
			Reasons for withdrawals	**Group 1:** • Inadequate IOP control = 1 • Conjunctivitis = 1 • Hyperaemia = 1 • Self-withdrawal = 1 **Group 2:** • Conjunctivitis = 1 • Hyperaemia = 1	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 50 **Age (mean ± SD):** 59 ± 13 **M/F:** 28/22 **POAG:** 50 **PXF:** 1* **Drop outs:** 4 * patient had different diagnosis in each eye			• Self-withdrawal = 2	**Notes:** If 2 eyes used in study, mean IOP was taken.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Separate combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Manni et al., 2004[91] **Study design:** RCT Single masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG **Setting:** Single centre, Italy **Inclusion criteria:** • COAG • At least 6 months current treatment with timolol 0.5% 2/day • Age >18 years • Best corrected visual acuity 20/80 or better • IOP ≥ 21 mmHg in at least 1 eye but at least 20 % lower than before any IOP lowering treatment. • Repeatable VF defect in same eye • **Exclusion criteria:** • Uncontrolled systemic diseases • Allergy to treatment medications • Severe trauma • Previous ocular surgery in last 6 months • Any condition affecting IOP measurement such as corneal abnormalities • Pregnant, nursing or patients considering pregnancy • **<u>All patients</u>** **N:** 61 **Age (mean ± SD):** 59.4 ± 14.1	**Group 1** Latanoprost 0.005% (pm) 1/day + Timolol 0.5% (am) 1/day **Group 2** Bimatoprost 0.03% 1/day evening **Examination methods:** IOP measured at baseline, 2 weeks and every month months using a Goldmann tonometer. 3 (8am, 12 pm, 4pm) measurements were taken in each eye and mean value used in statistical analysis. Photographs of lids and periocular area were taken at baseline to compare to end point	**Mean ± SD baseline diurnal IOP mmHg**	**Group 1:** 24.1 ± 4.6 **Group 2:** 23.5 ± 3.2	**Funding:** Not reported. Conducted at Clinica Oculistica, Universita di Roma Tor Vergata **Limitations:** • No washout period for bimatoprost monotherapy. • Patients were selected for inadequate IOP control on timolol 0.5% • *Significance testing between arms does not appear to be on an ITT basis – only 28 patients counted per group **Additional outcomes:** Occurrence of hyperaemia and eyelash growth **Notes:** Investigators were masked to treatment allocation and randomisation performed using computer generated sequence.
			Mean ± SD end point diurnal IOP at 6 mths	**Group 1:** 16.8 ± 1.4 **Group 2:** 17.0 ± 2.1	
			Mean ± SD reduction in IOP mmHg at 6mths (baseline – end point)	**Group 1:** 7.3 ± 5.59** **Group 2:** 6.5 ± 3.98** P = not significant*	
			Total number of patients reporting ocular side effects	**Group 1:** NR **Group 2:** NR	
			Total number of cardiovascular systemic side effects by group	**Group 1:** NR **Group 2:** NR 6 patients in group 1 reported a headache	
			Reasons for withdrawals	**Group 1:** • Inadequate IOP control = 2 • Ocular allergy = 2 **Group 2:** • Inadequate IOP control = 2 • Ocular allergy = 3 • Self-withdrawal = 2	
			Hyeperaemia at baseline	**Group 1:** 10/30 **Group 2:** 9/31 **P value:** 0.20	
			Hyeperaemia at 90 days	**Group 1:** 24/30 **Group 2:** 14/31 **P value:** 0.004	
			Hyeperaemia at 180 days	**Group 1:** 19/30 **Group 2:** 14/31 **P value:** 0.08	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 1 **N:** 30 **Age (mean ± SD):** 59.7 ± 13.5 **M/F:** 16/14 **Drop outs:** 4 **Group 2** **N:** 31 **Age (mean ± SD):** 59.2 ± 14.7 **M/F:** 14/17 **Drop outs:** 7				**Standard Deviations were estimated using the precise p values reported in the study following the method detailed in the Cochrane Handbook

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Separate combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Orengo-Nania et al, 2001[114] **Study design:** RCT, masked (subjects, investigators and study staff) **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG or OHT **Setting:** Multi-centre, USA **Inclusion criteria:** • Diagnosis of bilateral or unilateral POAG, pigmentary glaucoma (PG), pseudoexfoliation glaucoma (PXF) or OHT • Completed 3 weeks timolol 0.05% 2x/d • IOP in at least one eye of 24-36mmHg at 8am AND 21-36mmHg at 10am & 4pm; all 3 measurements on 2 eligibility days **Exclusion criteria:** • Best corrected visual acuity worse than 0.6 logMAR • chronic or recurrent severe inflammatory eye disease • ocular trauma in past 6 months • ocular infection or ocular inflammation in past 3 months • clinically significant progressive retinal disease • inability to undergo applanation tonometry • ocular disease precluding the use of beta-blockers or prostaglandins • cup to disc ratio >0.8 in either eye • severe central visual field loss • intraocular surgery in past 6 months • laser surgery in past 3 months • severe hypersensitivity to study	**Group 1** Travoprost 0.004% 1/day + timolol 0.5% 2/day * **Group 2** Placebo 1/day and timolol 0.5% 2/day * **Examination methods:** Mean IOP measured by calibrated Goldmann applanation tonometer at 8am, 10am and 4pm for the patient's eye with the highest reading. Hyperaemia measured by comparing photographs of subjects' eyes with a standard set of photographs depicting ocular hyperaemia. Hyperaemia and iris and eyelash	**Mean ± SD baseline diurnal IOP (mmHg)**	**Group 1:** 25.0 ± NR **Group 2:** 25.2 ± NR **P value:** not significant	**Funding:** Alcon Research Ltd, manufacturers of travoprost **Limitations:** Reporting of discontinuations was not clear for each group. 24 discontinued due to inadequate IOP control 21 in timolol group and 3 across both travoprost groups. Standard deviations were not provided with the IOP data. ***Timolol was open label*** **Additional outcomes:** Data for travoprost 0.0015% not included in study (dosage not in BNF) Eye lash changes also mentioned, no patient stopped treatment due to these. No reported iris
			Mean IOP at end point (6 months)	**Group 1:** 19.6 (8am), 18.3 (10am), 18.9 (4pm) **Group 2:** 23.8 (8am), 23.0 (10am), 23.1 (4pm)	
			Mean diurnal IOP at end point (6 months)	**Group 1:** 18.9 ± NR **Group 2:** 23.3 ± NR (calculated as mean across 3 times)	
			Mean change in IOP from baseline mmHg at 6 months (end point – baseline	**Group 1:** 6.1 ± NR **Group 2:** 1.9 ± NR P = 0.0001 (ANOVA – repeated measures)	
			Percent of patients with ≥6mmHg decrease in IOP OR ≤20mmHg at 6 mths	**Group1:** 73.0–86.9% **Group 2:** 23.1-43.3% (per protocol data)	
			Percent of patients with acceptable decrease ≥30% in IOP OR ≤17mmHg at 6 mths	**Group 1:** 55/114 (47.8%) **Group 2:** 11/112 (9.9%) **P value groups 1 to 2:** <0.0001 (per protocol data)	
			No. of ocular adverse events by group seen in ≥2% of any treatment group (NB some patients may have had more than one adverse event	**Group 1:** 78 **Group 2:** 34 Includes: aqueous flare, anterior chamber cells, blurred vision, discomfort, dry eye, foreign body sensation, hyperaemia, keratitis, lid disorder, pain, photophobia, pruritus, tearing, visual acuity decreased	
			No. of non-ocular adverse events by group seen in ≥2% of any treatment group	**Group 1:** 19 **Group 2:** 13 Includes: cold syndrome, infection, sinusitis, surgical/medical procedure,	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	medications or 'vehicle' • severe, unstable or uncontrolled cardiovascular, hepatic or renal disease in which the use of beta-blockers is contraindicated • bronchial asthma or COPD • Starting any medication that might affect IOP <1 month prior to study entry, glucocorticosteroid use during eligibility phase, current use of NSAIDs • glaucoma other than open-angle or ocular hypertension • anterior chamber angle grade < 2 • inability to use medication in both eyes • women who were not 1 year post-menopausal or had not been surgical sterilised 3 months before study **<u>All patients</u>** **N:** 271 **<u>Group 1</u>** **N:** 145 **Age (mean):** 63.9 ±11.1 **M/F:** 65/72 **Drop outs:** 8 **Black/Non-black:** 35/105 **COAG/OHT**: 123/14 **<u>Group 2</u>** **N:** 139 **Age (mean):** 63.3 ±11.3 **M/F:** 56/78 **Drop outs:** 5 **Black/Non-black:** 32/102 **COAG/OHT**: 121/13	changes were assessed by masked ophthalmologists.	(NB some patients may have had more than one adverse event)	urinary tract infection.	pigmentation changes or clinical visible cystoid macular oedema reported **Notes:** All subjects who qualified stopped any ocular hypotensive medication (other than timolol) and were placed on timolol 0.05% 2/day for 3 weeks. Run in phase Randomisation sequence was computer generated. Allocation concealment in sealed but not necessarily opaque envelopes.
			Number of patients with hyperaemia (assessed on a scale. 1=none/trace, 2=mild, 3=moderate, 4=severe. Mean hyperaemia score in all groups <0.50)	**Group 1:** 52/145 **Group 2:** 13/139 **P value groups 1 to 2**: <0.001	
			Reasons for withdrawals	**Group 1:** • NR **Group 2:** • Inadequate IOP control = 21	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Separate combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Polo et al., 2005[117] **Study design:** RCT **Evidence level:** 1 + **Duration of follow-up:** 24 months	**Patient group:** COAG **Setting:** Single centre, Italy **Inclusion criteria:** • POAG + Pseudoexfoliative Glaucoma (PXF) • Patients on monotherapy with beta blocker • Age >18 years • IOP ≥ 22 mmHg • Optic nerve head showing signs of glaucomatous damage **Exclusion criteria:** • Previous treatment of dorzolamide or latanoprost • Ocular infection or inflammatory disease in last 3 months • Allergy to treatment medications or preservative • Closed Angle Glaucoma • Previous ocular surgery or laser treatment in last 3 months • Cardiovascular or bronchial disease • Pregnant, nursing or patients considering pregnancy **<u>All patients</u>** **N:** 61 **<u>Group 1</u>** **N:** 30 **Age (mean ± SD):** 67.9 ± 11.2 **M/F:** 60%/40% eyes	**Group 1** Dorzolamide 2% 2/day + Timolol 0.5% 2/day **Group 2** Latanoprost 0.005% 1/day **Examination methods:** At eligibility testing, automated perimetry (Humphrey 30-II STATPAC 2) was used to measure visual field, stereo photographs used to assess glaucomatous damage (neuroretinal rim loss, haemorrhage etc), visual acuity, refraction, slit lamp examination also performed and IOP measurement technique was not specified. Examination schedule was at baseline, 2 wks and every 3 months.	**Mean ± SD baseline diurnal IOP mmHg**	**Group 1:** 23.8 ± 2.3 **Group 2:** 23.9 ± NR	**Funding:** Not reported. Conducted at Department of Ophthalmology, "Miguel Servet" University Hospital, Zaragoza, Spain **Limitations:** • Randomisation method not explained and no allocation concealment • Unmasked study, no placebo. • 3 week run in period on timolol • No drop out figures reported for patients • Not ITT analysis **Additional outcomes:** **Notes:** Data analyses use data per eye rather than patient. ** Standard deviations (SD) for fixed v monotherapy calculated using the Cochrane
			Mean ± SD end point diurnal IOP at 6 mths	**Group 1:** 18.2 ± 3.2 **Group 2:** 17.1 ± 2.4	
			Mean ± SD end point diurnal IOP at 24 mths	**Group 1:** 18.4 ± 1.9 **Group 2:** 15.9 ± 2.04	
			Mean ± SD reduction in IOP mmHg at 6 mths (baseline – end point)	**Group 1:** 5.6 ± 2.53** **Group 2:** 6.8 ± 1.94**	
			Mean ± SD reduction in IOP mmHg at 24 mths (baseline – end point)	**Group 1:** 5.4 ± 1.87** **Group 2:** 8.0 ± 1. 81** P < 0.05	
			Eyes reaching acceptable IOP of ≥ 20% reduction from baseline after 24 mths (<21 mmHg) *Figures estimated from Kaplan-Meier graph*	**Group 1:** 17/30 (56%) **Group 2:** 37/45 (82%)	
			Total number of patients reporting ocular side effects	**Group 1:** NR **Group 2:** NR	
			Total number of patients reporting cardiovascular systemic side effects	**Group 1:** NR **Group 2:** NR	
			Reasons for withdrawals	**Group 1:** NR **Group 2:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	1 eye/2eyes: 2/28 **Family history:** 24% eyes **POAG/PXF:** 23/8 **Drop outs:** 26/58 eyes (45%) **<u>Group 2</u>** **N:** 31 **Age (mean ± SD):** 64.6 ± 19.1 **M/F:** 64%/36% eyes **1 eye/2eyes:** 3/28 **Family history:** 29% eyes **POAG/PXF:** 25/5 **Drop outs:** 14/59 eyes (24%)				method for imputed SDs from the mean correlation coefficients calculated from Ozturk 2007[115] (CAI + BB v PGA)

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Separate combination vs. single medications (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rismanchian et al, 2008[121] **Study design:** RCT Observer masked **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** Newly diagnosed bilateral POAG **Setting:** single centre, ophthalmology department, Isfahan University of Medical Science, Feiz Hospital, Isfahan, Iran **Inclusion criteria:** • Diagnosis of unilateral or bilateral POAG with either visual field defects or optic nerve damage and elevated IOP ≥ 22 mmHg • Aged 18 or older • No previous treatment **Exclusion criteria:** • History of acute angle-closure or occludable angles • Contraindication to beta-blockers • Ocular surgery or argon laser trabeculoplasty • History of asthma, COPD, cardiac failure, sinus brachycardia, second or third degree atrioventricular block. • Severe renal impairment and hyperchloremic acidosis • Pregnant or breast feeding women • History of non-compliance or hypersensitivity to study drugs • Use of systemic medications affecting IOP **<u>All patients</u>** **N:** 120 **Age (mean ± SD):** 57.3 ± 13.15 (range 21-80) **M/F:** 60/60 **Drop outs:** NR **Group 1** **N:** 60	**Group 1** Dorzolamide 2% 3/day* & timolol 0.5% 2/day. *Note: normal dosage of dorzolamide if used with timolol is 2/day (BNF) **Group 2** Latanoprost 0.005% 1/day **Examination methods:** At baseline best corrected visual acuity, refraction, visual field testing, ophthalmoscopy, IOP measurement and slit lamp examination were performed. Goldmann applanation tonometry was used to measure IOP at 1, 3 and 6 months by same masked observer	**Mean ± SD IOP at 6 mths mmHg** **Mean ± SD change in IOP from baseline at 6 mths mmHg**	**Group1:** 22.9 ± 5.81 **Group 2:** 22.4 ± 5.42 **Group1:** 7.4 ± 2.32 **Group 2:** 7.1 ± 2.71 **p value:** 0.52 (calculated by NCC-AC team using t test with equal variances and ITT analysis)	**Funding:** Not reported **Limitations:** Randomisation method and allocation concealment not reported Dropouts were not reported so unclear if all patients completed study **Notes:** If both eyes qualified for study worse eye was used. No serious adverse events were observed.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean ± SD): 54.8 ± 15.49 (range 21-80) **M/F:** 28/32 **Drop outs:** NR **Mean Cup disc ratio ± SD:** 0.60 ± 0.15 **Mean baseline IOP ± SD mmHg:** 30.4 ± 6.58 **Group 2** **N:** 60 **Age (mean ± SD):** 52.7 ± 10.84 (range 35-80) **M/F:** 32/28 **Drop outs:** NR **Mean Cup disc ratio ± SD:** 0.60 ± 0.08 **Mean baseline IOP ± SD mmHg:** 29.6 ± 5.81				

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 14 Adverse events associated with topical medications

Study details	Patients	Interventions/ exposures	Outcome measures	Effect size	Comments
Kirwan et al, 2002[74] and Kirwan et al, 2004[75] **Country of study:** UK **Study design:** Retrospective cohort study **Evidence level:** 2+ **Duration of follow-up:** 12 months	**Patient group:** Elderly glaucoma patients with no previous diagnosis of airways obstruction identified from the Mediplus database. **Inclusion criteria:** • elderly patients but age not given **Exclusion criteria:** None reported **<u>All patients</u>** **N:** 11,739 **Age (mean):** NR **M/F:** NR **Additional risk factors:** NR **<u>Exposed group</u>:** **n:** 2645 **Age (mean):** 68.6 **<u>Unexposed group</u>:** **n:** 9094 **Age (mean):** 67.5	**Exposed group:** Patients who had used topical beta-blockers **Control group:** Patients randomly selected, loosely matched by age and gender to exposed group. Validated against a random sample of 40 full longitudinal records of exposed and unexposed patients.	**Patients given a new prescription of a drug for reversible airways obstruction for first time in the 12 months after treatment**	**Exposed:** 81/2645 (3.1%) **Control:** 112/9094 (1.2%) **Unadjusted hazard ratio:** 2.39 (95% CI: 1.79 to 3.20) * **Adjusted hazard ratio:** 2.29 (95% CI: 1.71 to 3.07) † **NNH:** 55 (95% CI: 29 to 85)	**Funding:** Not reported **Limitations:** Age cut off not given to describe elderly. Respiratory problems may not have always been done with an objective test . Consequently, the study reports that there may have been a certain rate of missed diagnosis or misdiagnosis diagnosis which may have underestimated the the true risk. **Notes:** * Adjusted analysis used a proportional hazards model, corrected for age, sex, use of systemic beta-blockers, use of non-steroidal anti-inflammatory drugs, use of nitrates, smoking, season of presentation, and number of visits to general practitioners. † Number of patients needed to be treated with topical beta-blockers to cause one case of airways obstruction during that time period.
			Patients given a new prescription of a drug for reversible airways obstruction for first time in the 6 months after treatment	**Exposed:** 49/2645 (1.9%) **Control:** 55/9094 (0.6%) **Unadjusted hazard ratio:** 2.83 (95% CI: 1.91 to 4.20) * **Adjusted hazard ratio:** 2.79 (95% CI: 1.88 to 4.15) † **NNH:** 84 (95% CI: 51 to 131)	
			Patients given a new prescription of a drug for reversible airways obstruction for first time in the 12 months after treatment AND a new Read code for asthma or COPD	**Exposed:** 191/2645 (7.2%) **Control:** 354/9094 (3.9%) **Unadjusted hazard ratio:** 1.81 (95% CI: 1.50 to 2.16) * **Adjusted hazard ratio:** 1.77 (95% CI: 1.48 to 2.12) † **NNH:** 30 (95% CI: 22 to 42)	
			Patients given a new prescription of a drug for reversible airways obstruction for first time in the 6 months after treatment AND a new Read code for asthma or COPD	**Exposed:** 115/2645 (4.3%) **Control:** 172/9094 (1.9%) **Unadjusted hazard ratio:** 2.16 (95% CI: 1.70 to 2.76) * **Adjusted hazard ratio:** 2.18 (95% CI: 1.71 to 2.79) † **NNH:** 42 (95% CI: 30 to 60)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Adverse events associated with topical medications (continued)

Study details	Patients	Interventions/ exposures	Outcome measures	Effect size	Comments
Kaiserman et al, 2006[68] **Country of study:** UK **Study design:** Cohort **Evidence level:** 2+ **Duration of follow-up:** All data for the years 2001 and 2003 assessed	**Patient group:** All patients aged over 20 who filled at least 6 consecutive antiglaucoma prescriptions at least once every 2 months in an Israeli health district. **<u>All patients</u>** **N:** 6597 **Age (mean):** NR **M/F:** NR **Additional risk factors:** NR **<u>Exposed group</u>:** **n:** 5846 **Age (mean):** 73.2 ±10.4 **M/F:** 2511/3335 **<u>Unexposed group</u>:** **n:** 751 **Age (mean):** 73.2 ±11.7 **M/F:** 331/420	**Exposed group:** Patients using beta-blockers alone or with another glaucoma medication Medications used include: Timolol, Betaxolol, Levobunolol or Dorzolamide-Timolol **Control group:** Patients using glaucoma medications other than beta-blockers Medications used include: Brimonidine, Dorzolamide, Latanoprost, Travoprost, Bimatoprost, Pilocarpine and others	**No. patients taking at least 4 prescriptions of anti-depressants**	**Exposed group:** 715/5846 **Control group:** 95/751 **p value:** 0.74 **Odds ratio (95% CI):** 0.96 (0.77 to 1.21)	**Funding** not reported **Additional outcomes reported:** Compared results by different age groups as age could be a confounder for glaucoma and depression. No significant differences were found between age groups. **Notes:** Included patients using at least 4 prescriptions of anti-depressants in order to dicount patients prescribed anti-depressants for brief reactive events.

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

Evidence Table 15 Laser treatment for COAG

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rolim & Paranhos, 2007[124] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum treatment 6 months but collected outcomes at 12 and 24 months where possible.	**Patient group:** POAG, primary & secondary pigmentary glaucoma, pseudoexfoliative glaucoma. **Inclusion criteria:** Any age, gender or nationality. RCTs only comparing laser trabeculoplasty with no intervention, with medical treatment, with surgery or comparing different modalities. **Exclusion criteria:** Studies with OHT patients **Primary Outcomes:** 1. Failure to control IOP 2. Failure to stabilise visual field 3. Failure to stabilise optic neuropathy **Secondary Outcomes:** 1. Necessity of adding or changing therapy or intervention when IOP is uncontrolled 2. Adverse Events (severe/minor) including: IOP spikes, Uveitis, cyclitis, hypoema, PAS formation, corneal oedema, persistent IOP elevation, loss of vision, bronchial spasm	**Comparison 2:** Argon laser trabeculoplasty (ALT) v medication in newly diagnosed participants **Studies included:** Gandolfi 2005, Moorfields (Migdal) 1994. **Comparison 3:** ALT v medication in participants already on maximal medical therapy. **Studies included:** Moriarty 1988 and Sherwood 1987. **Comparison 4:** ALT v trabeculectomy **Studies included:** AGIS 2002, Watson 1984 and Moorfields (Migdal) 1994. **Comparison 6:** Selective laser trabeculoplasty (SLT) v ALT **Studies included:** Damji 2006 Comparisons 2, 3, 4 and 6 are relevant to the clinical question "What is the effectiveness (and comparative effectiveness) of Laser Trabeculoplasty (ALT or SLT) in lowering IOP in patients with suspected or definite COAG (including POAG & NTG) **Intervention Details:**	**Comparison 2:** ALT v medication in newly diagnosed participants		**Funding:** Not stated. Conducted at the Universidade Federal de São Paulo, Brazil **Limitations:** Excludes OHT patients **Notes:** Literature search date to June 2007. Studies included in Rolim 2007 that are excluded from guideline **Bergea 1992** as both study arms received additional stepped medications including with timolol and acetazolamide. **Glaucoma Laser Trial (GLT)** because fellow eyes were randomised to ALT or medications
			Failure to Control IOP ≥22mmHg for Moorfields 1994 and Gandolfi 2005	***Relative Risk at 0-24 months*** Moorfields 1994 1.36 (95% CI: 0.50, 3.66) ***Relative Risk at 0 – 5 years*** Moorfields 1994 1.83 (95% CI: 0.93, 3.61) ***Relative Risk at 3-4 years*** Gandolfi 2005 1.20 (95% CI: 0.46, 3.15) (data not presented in Rolim)	
			Bronchial reactivity	Gandolfi. At 3 and 4 years there was a tendency for a reduced risk ratio in the ALT group but the figure was not statistically significant.	
			Comparison 3: ALT + Medication v Medication		
			Failure to Control IOP ≥21mmHg for Sherwood 1987 and ≥ 22mmHg for Moriarty 1988	***Relative Risk at 0-24 months*** Sherwood 1987 1.08 (95% CI: 0.02, 0.31) ***Relative Risk at 0-24 months*** Moriarty 1988 0.41 (95% CI: 0.22, 0.77)	
			Comparison 4: ALT v trabeculectomy		
			Failure to Control IOP ≥22mmHg for Moorfields 1994 and need for second intervention in sequence	***Relative Risk at 0-6 months*** AGIS & Moorfields 3.4 (95% CI: 1.60, 6.18) ***Relative Risk at 0-24 months*** AGIS & Moorfields 2.03 (95% CI: 1.38, 2.98)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	3. Quality of life measures 4. Economic data	ALT mainly performed with 50 µm spot, 50 – 100 burns, 0.8 to 2.0 Watts.0.1 sec exposure. **Quality Assessment:** ***Selection Bias*** – randomisation was adequately concealed in Watson 1984, AGIS, Moorfields (Migdal) 1994 and Damji 2006 ***Performance Bias*** - care providers and recipients could not be masked to intervention in most comparisons so criteria was not used ***Detection Bias*** - assessment of outcomes masked for AGIS and Gandolfi 2005 ***Attrition Bias*** – ITT analysis performed for AGIS and Damji 2006 and follow up described. Watson 1984 did not report loss to follow up. Moorfields (Migdal) 1994 was not an ITT analysis.	Optic neuropathy progression	Optic disc was photographed in Moorfields and Watson study but not reported	
			Comparison 6: Selective laser trabeculoplasty (SLT) v ALT		
			Failure to Control IOP	***Relative Risk at 12 months*** Damji 2006 1.27 (95% CI: 0.84, 1.90)	
			Mean ± SD score of flare in anterior chamber	SLT – 1.00 ± 0.6 ALT – 0.8 ± 0.6. Not signif.	

Abbreviations: NR=not reported, NA=not applicable, Signif =statistically significant at 5%, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE=Standard Error, AGIS – Advanced Glaucoma Intervention Study, Trab – Trabeculectomy, TAT – Trab then ALT then Trab, ATT – ALT then Trab then Trab, PAS - Peripheral Anterior Synechiae, ITT – Intention to Treat, FU – Follow Up

RCTs included in ROLIM 2007 that meet guideline inclusion criteria

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
AGIS 2002[1] [USA]	TAT v ATT	5 years	National Eye Institute, NIH, USA	Advanced POAG	591 (789)	67 median (35 - 80)	ALT: 24.0 ± 4.7 Trab: 24.6 ± 6.1	56 / 38	Selection: A Detection: D Attrition – FU: A Attrition – ITT: A Low risk of bias	Rolim includes results after 1st intervention in sequence only. Data obtained from study authors. Failure criterion is need for 2nd intervention in sequence
Damji et al., 2006[30] [Canada]	SLT V ALT	12 months	Lumenis (manufacturer of SLT)	COAG Uncontrolled IOP > 16 mmHg on max medication (38% previous ALT)	152 (176)	69.1 ± 10.52	ALT: 23.4 ± 4.2 SLT: 23.8 ± 4.9	NR/ NR	Selection: A Detection: D Attrition – FU: B Attrition – ITT: A Low risk of bias	Patients remained on current medications throughout follow up. Unacceptable IOP criteria ≥ 20 mmHg
Gandolfi et al., 2005[45] [Italy]	ALT V Timolol 0.5% 2/day	4 years	Research, Science & technology University, Rome	POAG with IOP ≥ 22 mmHg	32	44-67	ALT: 24.5 ± 2.0 Meds: 24.4 ± 1.5	NR/ NR	Selection: B Detection: D Attrition – FU:B Attrition – ITT: A Low risk of bias	Looks at respiratory adverse events but reports change in IOP from baseline. Number of patients with unacceptable IOP > 22mmHg excluded from study.
Migdal et al., 1994[98] Moorfields [UK]	ALT v Trab v Medical	6 mths - 8 years	Charity – Frost Foundation	COAG 29% early 23% middle 48% late	168 55 laser 57 Trab 56 Meds	63.5	ALT: 35.0 ± 8.7 Meds: 35.0 ± 5.4 Trab: 34.0 ± 5.4	6 / NR	Selection: A Detection: D Attrition – FU: A Attrition – ITT: B Low risk of bias	Data obtained from study authors Pilocarpine included in medications Unacceptable IOP criteria ≥ 22 mmHg
Moriarty et al., 1988[102] [Jamaica]	ALT + Medication V Medication	12 months	NR	POAG with IOP ≥22mmHg	30 (48)	62 (27-77)	ALT: 32.3 ± NR Meds: 29.2 ± NR	100/NR	Selection: B Detection: D Attrition – FU: C Attrition – ITT: A High risk of bias	Medication - pilocarpine 4% & oral acetazolamide 250mg; 4 patients also used timolol 0.5% Unacceptable IOP criteria ≥ 22 mmHg

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
Sherwood et al., 1987[136] [UK]	ALT + Medication V Medication	35 (30-40) months	Locally organised research scheme (GMC)	POAG with IOP >21mmHg	25 (50)	72.54 (50-90)	ALT: 23.8 ± NR Meds: 23.8 ± NR	NR/NR	Selection: A Detection: D Attrition – FU:A Attrition – ITT: A Low risk of bias	Medication - between minimum of 2 and maximum of 4 of the following: timolol, pilocarpine, sympathomimetics and acetazolamide Failure criteria ≥ 21 mmHg
Watson et al., 1984[159] [UK]	ALT v Trab	6 months	2 UK hospitals (Addenbrookes + Sunderland Eye Infirmary)	Severe COAG or evidence of progression not responding to medications	61 (95)	70 (38 – 86)	Site 1 ALT: 25.2 ± 5.5 Trab: 30.4 ± 8.6 Site 2 ALT: 33.7 ± 10.1 Trab: 39.5 ± 10.6	NR/ NR	Selection: A Detection: D Attrition – FU: C Attrition – ITT: C Moderate risk bias	Reports change in IOP from baseline for each treatment by hospital

Abbreviations: NR=not reported, NA=not applicable, Signif =statistically significant at 5%, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE=Standard Error, AGIS – Advanced Glaucoma Intervention Study, Trab – Trabeculectomy, TAT – Trab then ALT then Trab, ATT – ALT then Trab then Trab, PAS - Peripheral Anterior Synechiae, ITT – Intention to Treat, FU – Follow Up

Evidence Table 16 Trabeculectomy vs. pharmacological treatment

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Burr et al., 2004[15] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum length of follow-up was 12 months.	**Patient group:** POAG, NTG, pigmentary glaucoma, Pseudo-exfoliative glaucoma. **Inclusion criteria:** • Any gender or nationality • >18 years only **Possible interventions:** • Trabeculectomy ± MMC or 5F • Non-penetrating surgery ± MMC or 5F • Other surgery including drainage • Trans-scleral cytophotocoagulation (TSCPC) **Exclusion criteria:** Studies where medical arm included laser. **Primary Outcomes:** 4. Progressive visual field loss according to criteria described for each trial 5. Quality of Life **Secondary Outcomes:**	**Comparison 2:** Medications v trabeculectomy **Intervention Details:** **Surgery** Trabeculectomy in 3 Studies. Migdal 1994 (Moorfields Trial), Jay 1988 (Glasgow trial), Lichter 2001 (CIGTS trial) **Medications** Migdal 1994 (Moorfields Trial)- miotics, Sympathomimetic or beta-blocker + oral CAI Jay 1988 (Glasgow trial) - miotics, Sympathomimetic or beta-blocker + oral CAI Lichter 2001 (CIGTS trial) – Beta blockers + other not specified. **Quality Assessment:** ***Selection Bias*** – randomisation was adequately concealed in Lichter 2001 (CIGTS trial), Jay 1988 (Glasgow trial), Migdal 1994 (Moorfields Trial), ***Performance Bias*** - NR	**Comparison 1:** Medications v Scheie's procedure ***(no longer performed)***		**Funding:** Non industry funded (Cochrane Review). **Limitations:** • Includes Studies with miotics (pilocarpine). • Outcome assessment was not masked • Migdal 1994 (Moorfields) and Jay1988 (Glasgow trial) were not ITT analyses as the treatment failures had been excluded. **Notes:** Literature search date to August 2003. An updated search was run in February 2005 but no new studies were found. **Additional Outcomes:** Optic disc change (Jay 1988)
			Comparison 2: Medications v trabeculectomy		
			Progressive Visual Field Loss (Mean change in visual field score from baseline)	**Jay 1988 (Glasgow trial)** At 4.6 years mean follow-up 27/57 medical patients and 13/50 trab patients had progressed by at least one stage. **Migdal 1994 (Moorfields Trial)** Friedman Visual field analysis 3.92 (95% CI: 2.02 – 5.82) favours Trab. Signif Humphrey automated perimetry (introduced 2yrs after start of study) Medical: 25/40 (63%) progressed Trab:34/48 (71%) progressed OR:0.69 (95% CI: 0.29 – 1.67) No significant difference **Lichter 2001 (CIGTS trial)** VF Score change from baseline – 1yr -0.5 (95% CI: -1.10 – 0.10) VF Score change from baseline – 5yr 0.30 (95% CI: -0.45 – 1.05) No significant difference at 1 or 5yrs ANOVA Mean VF score difference between treatment groups over follow up time -0.36 (95% CI: -0.67 to -0.05) Adjusting for cataract mean VF: -0.28 (95% CI: -0.59 to 0.03) No significant difference Logistic Regression (adjusting for baseline VR, age, sex, race, diagnosis, diabetes and time in study) Risk of progressive VFL of at least 3 units from baseline	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	5. Change in IOP 6. Progression of optic disc or nerve fibre damage 7. Reduction of LogMAR score ≥ 0.3 (Snellen visual acuity ≥ 2 lines) 8. Adverse Events (severe/minor) including: mortality, loss of eye due to infection or inflammation, severe irreversible reduction in vision, visually significant cataract, incidence of cataract surgery, need for additional surgery or medication, transient decrease in central vision from complications, systemic side effects (cardiovascular and COPD, CNS defects), local side effects (eye irritation, watering, redness, discomfort) 9. Economic data	***Detection Bias*** - Assessment of outcomes was not masked for any of the Studies apart from QoL in CIGTS – telephone administered questionnaire ***Attrition Bias*** Jay 1988 (Glasgow trial): 25/57 in medication group and 30/50 not available for final analysis. IOP analysis not ITT Migdal 1994 (Moorfields Trial): IOP and VF analysis not ITT. Lichter 2001 (CIGTS trial): at 5 years 37/607 lost to follow-up. Analysis was ITT		between treatment groups: OR= 0.74 (95% CI: 0.54 – 1.01) Adjusted for cataract: OR = 0.75 (95% CI: 0.55 – 1.02) No significant difference	Health related quality of life in Lichter 2001 (CIGTS trial) Economic measures in Migdal 1994 (Moorfields Trial) Visual Acuity Loss (All studies) Burr 2004 reported OR for VF progression for CIGTS and also Number of patients with unacceptable IOP for Moorfields but did not did not actual dichotomous outcome figures so they could not be included in the meta-analysis. Jampel et al., 2005[64] paper describes perioperative complications for the CIGTS study and reports number of trabs with no augmentation = 177/465 eyes, Number with 5FU = 266/465 eyes and number with MMC = 22/465 eyes
			Mean reduction in IOP from baseline mmHg	**Jay 1988 (Glasgow trial) [short term only]** 6.0 (95% CI:2.64 – 9.36) **Migdal 1994 (Moorfields Trial)** **Short term** (51/56 Medical/Surgery) 6.2 (95% CI: 3.92 – 8.48) **Medium term** (50/56 Medical/Surgery) 1.6 (95% CI: -0.69 – 3.89) **Long term** (46/56 Medical/Surgery) 3.4 (95% CI: 1.04 – 5.76) [Both above studies exclude failures from the point of failure]. **Lichter 2001 (CIGTS trial)** At year one (595 pts) 3.6 (95% CI: 2.78 – 4.42) Favours Trab Signif At 5 years (384 pts) 1.9 (95% CI: 0.85 – 2.95) Favours Trab. No significant difference.	
			Adverse Events	**1) Mortality** **Jay 1988 (Glasgow trial)** At last follow up (mean 4.6yrs) 12/112 (14%) of recruited pts died. 7in the medical group, 8 in the Trab group and 1 unknown. **2) Severe irreversible reduction in vision** **Jay 1988 (Glasgow trial)** At one year, 6/46 (13%) eyes in the medical group had lost central fixation and in the following 2 years, a further 2 in the same group. No pts in the Trab group lost central fixation over mean follow up of 33 months. **3) Visually significant cataract** **Total from all Studies** 57/403 for trabeculectomy	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
				24/416 for medications. RR: 2.45 (95% CI: 1.55 to 3.87)	

Abbreviations: NR=not reported, M/F=male/female, NA=not applicable, N=total number of patients randomised, SD=Standard Deviation, CI95%= 95% Confidence Interval, ITT=Intention to Treat

RCTs included in BURR 2004 that meet guideline inclusion criteria

STUDY	Intervention	Duration	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean Baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
Jay & Murray, 1988[65] Glasgow [UK]	Trab v Medical	7yrs max (mean 4.6yrs)	NR	Newly diagnosed POAG 65% moderate 35% severe	107 50 Trab 57 Meds	NR	Meds: 37.8 ± NR Trab: 37.8 ± NR	0/ NR	Selection: A Detection: C Attrition – FU: B Attrition – ITT: C Moderate risk of bias	*Outcome assessment was not masked* *Pilocarpine included in medication* *Treatment failures excluded from analysis*
Lichter et al., 2001[89] CIGTS **[USA]**	Trab v Medical	Min 5 yrs	Non industry – National Institutes of Health, National Eye Institute grants	91% POAG (mean visual field defects 4.8units on a scale of 0 to 20) C/D range 0.6-0.7 Mild glaucoma	607 300 Trab 307 Meds	57.5 (range 28-75)	Meds: 27 ± NR Trab: 27 ± NR	44 / NR	Selection: A Detection: C Attrition – FU: A Attrition – ITT: A Low risk of bias	*Main medication was beta-blockers*
Migdal et al., 1994[98] Moorfields [UK]	ALT v Trab v Medical	6 mths - 8 yrs	Charity – Frost Foundation	COAG 29% early 23% middle 48% late	168 55 laser 57 Trab 56 Meds	63.5	ALT: 35.0 ± 8.7 Meds: 35.0 ± 5.4 Trab: 34.0 ± 5.4	6 / NR	Selection: A Detection: C Attrition – FU: B Attrition – ITT: C Moderate risk of bias	*Outcome assessment was not masked* *Data obtained from study authors* *Pilocarpine included in medications* *Failure criteria ≥ 22 mmHg* *Treatment failures excluded from analysis*

Cochrane Quality Assessment Grades: A =Acceptable, B=Unclear, C=inadequate

Evidence Table 17 Trabeculectomy plus pharmacological augmentation vs. trabeculectomy

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Wilkins et al., 2005[161] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum follow up 12 months	**Patient group:** POAG, pigmentary glaucoma, pseudoexfoliative glaucoma, closed-angle glaucoma and other secondary glaucomas – congenital, neovascular etc 3 population sub-groups considered: 1. High risk of failure – previous drainage surgery, cataract surgery or with secondary glaucomas 2. Combined surgery with extra-capsular cataract extraction and intraocular lens implantation. 3. Primary trabeculectomy **Inclusion criteria**: RCTs with intraoperative Mitomycin C (MMC) administered at any concentration or dose compared to placebo or control. **Primary Outcomes:** 6. Proportion of failed surgeries at 12 months post-surgery (failure defined as repeat surgery or uncontrolled IOP despite additional medications) 7. Mean IOP at 12 months **Secondary Outcomes:** 10. Wound leaks detected by positive Seidel test	**Intervention Details:** Surgery was performed with or without Mitomycin C delivered intraoperatively at concentrations of 0.1 – 0.5 mg/ml saline for between 1 and 5 minutes. **Quality Assessment:** ***Selection Bias*** – randomisation and allocation concealment was graded as A adequate, B unclear or C inadequate, only studies with A or B were included ***Performance Bias*** - checking whether recipients or those providing care were masked to treatment allocation. If not then study deemed as high risk of bias. ***Detection Bias*** - checking whether assessment of outcomes was masked. If not then study deemed as high risk of bias. ***Attrition Bias*** – checking	**Failure at 12 months Primary Trabeculectomy** (338 patients)	Costa 1996, Martini 1997, Robin 1997, Szymanski 1997 **Relative Risk**: 0.37 in favour of MMC **Signif.** (CI 95% 0.26 – 0.51) **p value**: 0.00004	**Funding:** MRC and Moorfields Eye Hospital **Limitations:** • Includes trials a proportion of patients with closed-angle glaucoma (CACG). • Includes secondary glaucomas such as congenital, neovascular, uveitic, traumatic etc **Notes:** Latest literature search to March 2005 Studies included in Wilkins 2005 that are excluded from guideline **Andreanos 1997** includes high patients with previous surgery **Carlson 1997** includes combination cataract surgery **Shin 1995** includes combination cataract surgery **Shin 1998** includes high patients with previous surgery and combination cataract surgery **Cohen 1996** includes CACG but proportion is not defined **Turacli 1996** – includes 17% closed-angle glaucoma patients & 22% secondary glaucomas (congenital, neovascular etc) **Wu 1996** – secondary glaucomas
			Mean IOP at 12 months Primary Trabeculectomy	Costa 1996, Martini 1997, Szymanski 1997 **Weighted Mean Difference:** 5.41 mmHg in favour of MMC **Signif.** (CI 95% 7.34 – 3.49) **p value**: <0.00001 Robin 1997 did not report IOP at 12 months	
			Wound leak	**Primary Trabeculectomy** Szymanski 1997 **Odds Ratio**: 1.65 in favour of control **Not signif.** (CI 95% 0.16 – 17.47) **p value**: 0.7	
			Hypotony	**Primary Trabeculectomy** Costa 1996, Martini 1997, Szymanski 1997 **Odds Ratio**: 1.05 in favour of control **Not signif.** (CI 95% 0.23 – 4.68) **p value**: 1.0	
			Expulsive Haemorrhage	***No events reported***	
			Cataract	**Primary Trabeculectomy** Costa 1996, Martini 1997, Szymanski 1997, Robin 1997 **Relative Risk**: 1.93 in favour of control **Not signif.** (CI 95% 0.98 – 3.80) **p value**: 0.6	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	11. Hypotony IOP < 5 mmHg 12. Late endophthalmitis infection 13. Expulsive or choriodal haemorrhage 14. Shallow anterior chamber 15. Cataract – reduction in optical clarity 16. Quality of Life assessments and patients perspectives	whether analysis was done on an ITT basis and if rates of follow up were similar in each group. If not then study deemed as high risk of bias.	**Shallow Anterior Chamber**	**Primary Trabeculectomy** Costa 1996, Martini 1997 **Odds Ratio**: 1.14 in favour of control **Not signif.** (CI 95% 0.42 – 3.07) **p value**: 0.8	(congenital, neovascular etc)

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Wormald et al., 2001[162] **Study design:** Systematic Review **Evidence level:** 1++ **Duration of follow-up:** Minimum follow up 12 months	**Patient group:** POAG, pigmentary glaucoma, pseudoexfoliative glaucoma, closed-angle glaucoma and other secondary glaucomas – congenital, neovascular etc 3 population sub-groups considered: 4. High risk of failure – previous drainage surgery, cataract surgery or with secondary glaucomas 5. Combined surgery with extra-capsular cataract extraction and intraocular lens implantation. 6. Primary trabeculectomy **Inclusion criteria:** RCTs with postoperative 5-Fluorouracil (5-FU) administered injections at any concentration or dose compared to placebo or control. **Primary Outcomes:** 8. Proportion of failed surgeries at 12 months post-surgery (failure defined as repeat surgery or uncontrolled IOP > 22 mmHg despite additional medications) **Secondary Outcomes:** 17. Wound leaks detected by positive Seidel test 18. Hypotony IOP < 5 mmHg 19. Late endophthalmitis infection 20. Expulsive or choroidal haemorrhage	**Intervention Details:** Surgery was performed with or without postoperative injections of 5-FU in 0.1 or 0.5 ml saline solution **Quality Assessment:** A quality score was applied to each study 1. Clear description of inclusion/exclusion criteria (YES-1/NO-0) 2. Was study randomised? (YES with description-2/ONLY STATED – 1/NO-0) 3. Was study double blind? (YES with description-2/ONLY STATED – 1/NO-0) 4. Was there a description of withdrawals & dropouts? (YES-1/NO-0) 5. Were statistics methods described? (YES-	**Failure at 12 months Primary Trabeculectomy** (338 patients)	Goldenfeld 1994, Ophir 1992 **Relative Risk:** 0.21 in favour of 5-FU **Signif.** (CI 95% 0.06 – 0.68) **p value:** 0.009	**Funding:** Moorfields Eye Hospital **Limitations:** • Includes trials a proportion of patients with closed-angle glaucoma (CACG). • Includes secondary glaucomas such as congenital, neovascular, uveitic, traumatic etc **Notes:** Latest literature search to January 2008 – no new studies to add Studies included in Wormald 2001 that are excluded from guideline **Gandolfi 1997** includes combination cataract surgery **Loftfield 1991** conference abstract **FFSSG 1996** 32% Secondary angle-closure glaucoma and 33% other types including secondary open-angle, pigmentary glaucoma and primary angle closure glaucoma (proportions not specified) **O'Grady 1993** includes combination cataract surgery **Ruderman 1987** includes 69% secondary glaucomas (congenital, neovascular etc)
			Mean IOP at 12 months Primary Trabeculectomy	Goldenfeld 1994, Ophir 1992 **Weighted Mean Difference:** 4.67 mmHg in favour of 5-FU **Signif.** (CI 95% 2.74 – 6.60) **p value:** <0.00001	
			Wound leak	**Primary Trabeculectomy** Goldenfeld 1994, Ophir 1992 **Relative Risk:** 0.47 in favour of 5-FU **Not Signif.** (CI 95% 0.04 – 4.91) **p value:** 0.5	
			Hypotonous maculopathy	**Primary Trabeculectomy** Goldenfeld 1994, **Relative Risk:** 2.82 in favour of control **Not Signif.** (CI 95% 0.12 – 66.62)	
			Endophthalmitis	***No events reported***	
			Cataract	**Primary Trabeculectomy** Chaudhry 2000 **Relative Risk:** 6.00 in favour of control **Not signif.** (CI 95% 0.76 – 47.49)	
			Shallow Anterior Chamber	**Inconsistently reported among trials**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	21. Shallow anterior chamber 22. Corneal and conjunctive epithelial erosions	1/NO-0) Allocation concealment was also assessed as A-adequate, B-unclear, C-inadequate			**Wong 1994** includes combination cataract surgery

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Egbert et al., 1993[39] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** Mean approx. 9 months	**Patient group:** West African patients with advanced POAG, CACG & traumatic glaucoma **Setting:** single centre - Ghana **Inclusion criteria:** • Non-phakic glaucoma **Exclusion criteria:** NR **<u>All patients</u>** **N:** 59 (61 eyes) **Age (mean ± SD):** NR **M/F:** 35/20 **Mean IOP:** NR **Drop outs:** NR **<u>Group 1</u>** **N:** 31 **Age (mean ± SD):** 58.9 (range 22-83) **M/F:** 23/8 **Eyes with previous operations:** 4 **Mean IOP:** 33.4 (range 16-76) **Drop outs:** NR **<u>Group 2</u>** **N:** 24 **Age (mean ± SD):** 60.6 (range 36-76) **M/F:** 12/12 **Mean IOP:** 29.2 (range 18-46) **Drop outs:** NR	**Group 1** Trabeculectomy **Group 2** Trabeculectomy + Intraoperative 5-Flourouracil (5-FU) 50 mg/ml for 5 minutes on surgical sponge **Examination methods:** ***Preoperative:*** Visual acuity, slit lamp examination, Goldmann tonometry, gonioscopy and ophthalmoscopy. ***Postoperative:*** Visual acuity, slit lamp examination, Goldmann tonometry Day 1, and over 1st week. Other follow-up visits were irregular.	**Mean IOP at final visit (mean follow-up 9 months)**	**Group 1:** 24.5 (range 4-74) **Group 2:** 17.3 (range 6-35) **p value:** 0.05 (Mann-Whitney U test)	**Funding:** Partially funded by Research to Prevent Blindness - USA **Limitations:** • West African population only • Includes 4% CACG patients & 4% traumatic glaucoma patients • 61 eyes started study but only 55 were included in the analysis. Dropouts per group not reported. • Follow up time is limited. Complications such as bleb infections could increase in the 5-FU group with longer follow up. • Randomisation method, allocation concealment and masking of outcome assessment were not mentioned. **Additional outcomes:** Visual acuity **Notes:** No postoperative 5FU injections were performed
			Number of eyes with acceptable IOP (<20 mmHg without medications at 12 months	**Group 1:** 10/31 **Group 2:** 17/24 **p value:** 0.02 **signif.**	
			Number of eyes with unacceptable IOP >20mmHg at end point (9 mths)	**Group 1:** 21/31 **Group 2:** 7/24 **p value:** NR	
			Number of eyes with unacceptable IOP >15mmHg at end point (9 mths)	**Group 1:** 26/31 **Group 2:** 13/24 **p value:** NR	
			Number of patients on postoperative medications	**Group 1:** 16 (46%) **Group 2:** 5 (24%) **p value:** 0.02 (Chi-squared) **signif.**	
			Hyphaema	**Group 1:** 1/31 **Group 2:** 0/24 **p value:**	
			Cataract progression	**Group 1:** 3/31 **Group 2:** 4/24 **p value:**	
			Flat anterior chamber	**Group 1:** 2/31 **Group 2:** 2/24 **p value:**	
			Conjunctival wound leak	**Group 1:** 2/31 **Group 2:** 4/24 **p value:** Not signif.	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Corneal epithelial defects	**Group 1:** 0/31 **Group 2:** 0/24 **p value:**	

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Leyland et al., 2001[88] **Study design:** RCT **Evidence level:** 1+ Double blind **Duration of follow-up:** 30	**Patient group:** POAG, chronic closed-angle glaucoma & pseudoexfoliative glaucoma **Setting:** single centre - UK **Inclusion criteria:** • POAG, CACG (13%), PXF • Established disc cupping and glaucomatous field loss • Uncontrolled IOP • ≥ 18 years **Exclusion criteria:** • Other glaucomas such as congenital, uveitic, traumatic • Previous surgery • Laser treatment within last 6 months • Pregnant women **<u>All patients</u>** **N:** 39 (43 eyes) **Age (mean ± SD):** NR **M/F:** 35/20 **Mean IOP:** NR **Drop outs:** 3 **<u>Group 1</u>** **N:** 17 **Age (mean ± SD):** 66.7 ± 11.4 **M/F:** 10/7 **Mean IOP:** 28.1 ± 6.8 **Visual Field (Mean Db):** -15.1 ± 10.1 **Drop outs:** 2 **<u>Group 2</u>**	**Group 1** Trabeculectomy + 0.9% Sodium Chloride for 5 minutes on surgical sponge **Group 2** Trabeculectomy + Intraoperative 5-Flourouracil (5-FU) 25 mg/ml for 5 minutes on surgical sponge **Examination methods:** ***Postoperative:*** Visual acuity, bleb appearance, IOP, lens clarity and fundus appearance monitored at each visit at 1 day, 1 week, 1, 3, 6, 12 months.	**Mean IOP at 12 months**	**Group 1:** 15.3 ± NR **Group 2:** 14.7 ± NR **p value:** Not signif.	**Funding:** NR **Limitations:** • Includes 5/40 (13%) CACG patients • Primary outcomes not reported **Additional outcomes:** Bleb analysis **Notes:** 1 postoperative 5FU injections was performed on a patient in group 1 Double blind study with allocation concealment
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	**Group 1:** NR **Group 2:** NR **p value:**	
			Cataract progression (late surgery)	**Group 1:** 4/17 **Group 2:** 5/23 **p value:**	
			Shallow anterior chamber	**Group 1:** 3/17 **Group 2:** 7/23 **p value:** 0.06	
			Conjunctival wound leak	**Group 1:** 3/17 **Group 2:** 7/23 **p value:**	
			Corneal punctate epithelial keratopathy	**Group 1:** 3/17 **Group 2:** 5/23 **p value:**	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 23 **Age (mean ± SD):** 64.8 ± 12.2 **M/F:** 10/7 **Mean IOP:** 27.7 ± 5.7 **Visual Field (Mean Db):** -14.4 ± 9.1 **Drop outs:** 1				

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Trabeculectomy plus pharmacological augmentation vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
RASHEED, 1999[118] **Study design:** RCT (single blind) **Evidence level:** 1 + **Duration of follow-up:** 18 months	**Patient group:** POAG & CACG **Setting:** single-centre - Egypt **Inclusion criteria:** Bilateral POAG or CACG (16%) uncontrolled on medical therapy **Exclusion criteria:** None detailed **All patients** **N:** 25 (50 eyes) **Age (mean):** 50.3 ± 14.1 **M/F:** 12/13 **Mean IOP:** NR **Drop outs:** 0 **Group 1** **N:** 25 **Age (mean):** see above **M/F:** see above **Mean IOP:** 28.1 ± 3.14 **Pre-op Medications:** 3.7 ± 0.3 **Drop outs:** 0 **Group 2** **N:** 25 **Age (mean):** see above **M/F:** see above **Mean IOP:** 28.0 ± 3.19 **Pre-op Medications:** 3.7 ± 0.6 **Drop outs:** 0	**Group 1** Trabeculectomy **Group 2** Trabeculectomy + Mitomycin C. 0.3 – 0.4 mg/ml for 4 minutes depending on risk of failure **Examination methods:** Not clearly stated but infer that IOP, changes in optic disc and VF progression measured.	**Mean IOP during last 6 months of study (months 12-18)**	**Group 1:** 16.1 ± 5.1 **Group 2:** 10.2 ± 3.9 **p value:** NR	**Funding:** NR **Limitations:** • Includes 4/25 (16%) CACG patients • States as single blind though no details given • Some discrepancies in the statistical tests • Allocation concealment and masking of outcome assessment not reported **Additional outcomes:** Argon laser suture lysis **Group 1:** 21/25 **Group 2:** 13/25 **Notes:** Computerised randomisation Fellow eyes randomised
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	**Group 1:** 12/25 (48%) **Group 2:** 21/25 (84%) **p value:** NR *p = 0.016 Fishers Exact calculated by NCC-AC as ITT (n=25 in both groups)*	
			Number of eyes with unacceptable IOP >20mmHg at 12 months	**Group 1:** 17/25 **Group 2:** 7/25 **p value:** NR	
			Hyphaema	**Group 1:** 2/25 **Group 2:** 2/25 **p value:**	
			Cataract progression	**Group 1:** 1/25 **Group 2:** 1/25 **p value:**	
			Wound leak	**Group 1:** 3/25 **Group 2:** 10/25 **p value:** 0.44 (Chi-squared) *p = 0.051 Fishers Exact calculated by NCC-AC as ITT (n=25 in both groups)*	
			Bleb scarring	**Group 1:** 6/25 **Group 2:** 1/25 **p value:** 0.04 (Chi-squared) *p = 0.1 Fishers Exact calculated by NCC-AC as ITT (n=25 in both groups)*	

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Summary of RCTs included in WORMALD 2001 and WILKINS 2005 that met guideline inclusion criteria

STUDY	Intervention MMC	Duration (months)	Funding	Population Disease severity	Size N - patients (eyes)	Age (mean/ range)	Mean baseline IOP mmHg	% Afro-Caribbean / % Family History	Cochrane Quality Check	Notes
Costa et al., 1996[26] [Brazil]	0.2 mg/ml for 3 minutes v Placebo	18	NR	Medically uncontrolled POAG + ***14% CACG***	28 (28)	67.0	MMC: 26.35 ± 6.68 Placebo: 24.92 ± 7.07	32 / NR	Allocation concealment – B unclear	Primary trabeculectomy Randomisation unclear Double masked Failure criteria >15 mmHg without medication
Goldenfeld et al., 1994[49] [Israel]	5 x 1/day 5 mg injections over first 15 postoperative days	20	Partially by Research to Prevent Blindness	Medically uncontrolled POAG or PXF	62 (62)	67.3 range (46 - 84)	5-FU: 25.0 ± 6.22 NT: 27.4 ± 12.05	10 / NR	Quality Score = 4 Allocation concealment – B unclear	Randomisation was adequate but, allocation concealment and masking of outcome assessment were not reported. Failure criteria >21 mmHg with medications
Martini et al., 1997[94] [Italy]	0.1 mg/ml for 3 minutes v NT	12	NR	Medically uncontrolled COAG	48 (60)	65.5	MMC: 28.8 ± 7.4 NT: 28.4 ± 9.2	NR / NR	Allocation concealment – B unclear	Computer randomisation Investigator masked Failure criteria >18 mmHg with or without medication. Some patients had previous laser treatment
Ophir & Ticho 1992[113] [Israel]	5 x 1/day 5 mg injections over first 10 postoperative days	18	NR	Medically uncontrolled POAG + **18% CACG**	50 (50)	63.2	5-FU: 25.7 ± 2.1 NT: 25.9 ± 2.4	48 / NR	Quality Score = 1 Allocation concealment – B unclear	Randomisation, allocation concealment and masking of outcome assessment were not reported. Failure criteria >20 mmHg with medications
Robin et al., 1997[123] [USA]	MMC 1 - 0.2 mg/ml for 2 mins MMC 2 - 0.2 mg/ml for 4 mins MMC 3 – 0.4 mg/ml for 2 mins	12	NR	Medically uncontrolled COAG + ***39% CACG***	300 (300)	57	T: 29.1 ± NR MMC 1: 28.1 ± NR MMC 2: 30.6 ± NR MMC 3: 30.9 ± NR	NR / NR	Allocation concealment –A adequate	Double masked study Failure criteria >19 mmHg with or without medication. Some patients had previous laser treatment
Szymanski et al., 1997[147] [Poland]	0.2 mg/ml or 0.5 mg/ml for 5 min v Placebo	18	NR	Medically uncontrolled POAG	29 (29)	47.8	All: 21.6 ± 4.2	NR / NR	Allocation concealment – B unclear	Randomisation, allocation concealment, masking of outcome assessment not reported. IOP control is not primary outcome Failure criteria >15 mmHg with medication

Abbreviations: NR = not reported, NA = not applicable, Signif = statistically significant at 5%, M/F = male/female, N = total number of patients randomised, SD = Standard Deviation, SE=Standard Error, K-M = Kaplan-Meier, NT = No Treatment, MMC – Mitomycin C, 5FU – 5-Fluorouracil

Evidence Table 18 Trabeculectomy plus antimetabolite drug MMC vs. antimetabolite drug 5-FU

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Singh et al., 1997[138] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** mean 10.0±4.41 months (difference between groups p=0.70)	**Patient group:** West African POAG patients **Setting:** Cape Coast Christian Eye Clinic, Ghana **Inclusion criteria:** Diagnosis of POAG based on visual acuity, slit lamp examination, Goldmann applanation tonometry, gonioscopy and post dilation ophthalmoscopy **Exclusion criteria:** NR **<u>All patients</u>** **N:** 81 **Age (mean ± SD):** 53.6 P-value for diff = 0.73 **M/F:** 49/32 P-value for diff = 0.29 **Mean IOP:** 30.1 (17-55) P-value for diff = 0.46 **Drop outs:** 0 **<u>Group 1</u>** **N:** 44 **Age (mean ± SD):** 54.1 **M/F:** 29/15 **Mean IOP:** 30.7 (20-47) **Drop outs:** 0	**Group 1** Primary trabeculectomy with intraoperative use 0.5mg/ml MMC for 3.5 minutes on a soaked surgical sponge wedged between the flap and the conjunctiva. **Group 2** Primary trabeculectomy with intraoperative use 50 mg/ml 5-FU for 5 minutes on a soaked surgical sponge wedged between the flap and the conjunctiva. **Examination methods:** 90-diopter lens at the slit lamp examination and applanation tonometry. Indirect ophthalmoscopy was reserved for eyes with unexplained vision loss or shallow anterior chamber. Visits were at 3, 7, and 14 days postoperatively.	**Mean (range) IOP at follow-up (mmHg) at mean follow-up of 10 months**	**Group 1:** 13.7 (2-30) **Group 2:** 16.3 (4-36) **p value:** 0.05 (Chi-square test)	**Funding:** NR **Limitations:** • Patients and medical staff were not kept blind • Only partially applicable (West African patients) • Only 81 of the 85 patients randomised were followed up for at least 3 months postoperatively. **Notes:** The surgical technique and postoperative care did not vary for individual surgeons based on choice of antimetabolites. Randomisation by coin flipping prior to surgery **Additional outcomes:** 22/44 in the MMC group and 23/37 in the FU group had preoperative visual acuity of 6/60 or worse in the treated eye. .
			IOP success (with or without medications – not explicitly stated) at mean follow-up of 10 months	**IOP < 21mmHg** **Group 1:** 41/44 (93.2%) **Group 2:** 27/37 (73.0%) **p value:** 0.01 (Chi-square test) **IOP < 18mmHg** **Group 1:** 31/44 (70.5%) **Group 2:** 21/37 (56.8%) **p value:** 0.21 (Chi-square test) **IOP < 15mmHg** **Group 1:** 28/44 (63.6%) **Group 2:** 19/37 (51.4%) **p value:** 0.26 (Chi-square test)	
			Number of patients with unacceptable IOP (with or without medications – not explicitly stated) at mean follow-up of 10 months	**IOP > 21mmHg** **Group 1:** 3/44 (93.2%) **Group 2:** 10/37 (73.0%) **p value:**	
			Proportion of patients taking IOP-lowering medication at final follow-up	**Group 1:** 10/44 **Group 2:** 9/37 **p value:** 1 (Fisher's exact calculated by NCC-AC)	
			Eyes with no change in postoperative visual acuity	**Group 1:** 32/44 **Group 2:** 27/37 **p value:** 0.96 (Chi-square test)	
			Eyes with more than two-line decrease in	**Group 1:** 6/44 **Group 2:** 7/37	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 37 **Age (mean ± SD):** 52.7 **M/F:** 20/17 **Mean IOP:** 32.0 (22-45) **Drop outs:** 0		**visual acuity**	**p value:** 0.53 (Chi-square test)	
			Flat anterior chamber	**Group 1:** 1/44 **Group 2:** 0/37 **p value:** 1 (Fisher's exact calculated by NCC-AC)	
			Cataract	**Group 1:** 3/44 **Group 2:** 3/37 **p value:** 1 (Fisher's exact calculated by NCC-AC)	
			Hypotony (IOP<6mmHg)	**Group 1:** 2/44 **Group 2:** 2/37 **p value:** 1 (Fisher's exact calculated by NCC-AC)	
			Persistent wound leak	**Group 1:** 0/44 **Group 2:** 0/37 **p value:** NA	
			Endophthalmitis	**Group 1:** 0/44 **Group 2:** 0/37 **p value:** NA	

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, IOP=intra-ocular pressure, POAG=primary open-angle glaucoma, MMC=mitomycin, 5-FU=5-Fluorouracil, VA=visual acuity

Trabeculectomy plus antimetabolite drug MMC vs. antimetabolite drug 5-FU (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Zadok et al., 1995[165] **Study design:** RCT Investigator who followed up the patients was masked to intervention. **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** Single centre in Israel. **Inclusion criteria:** Adult patients with medically uncontrolled POAG. **Exclusion criteria:** NR **<u>All patients</u>** **N:** 20 (20 eyes) **Age (mean):** NR **M/F:** 11/9 **Mean IOP:** see below. P-value for diff = 0.22. **Drop outs:** 0 **<u>Group 1</u>** **N:** 10 **Age (mean):** 70.8±8.0 **M/F:** 7/3 **Mean IOP:** 24.0±1.9 **Drop outs:** 0 **<u>Group 2</u>** **N:** 10 **Age (mean):** 66.6±7.6 **M/F:** 4/6 **Mean IOP:** 25.7±3.8 **Drop outs:** 0	**Group 1** Cairn's filtering procedure in which a surgical sponge soaked in a 0.2mg/ml MMC was placed between the conjunctiva and episclera for five minutes. The tissues were then rinsed with 100ml of balanced salt solution. **Group 2** Cairn's filtering procedure in which 5 mg of 5-FU (0.5ml of a 10 mg/ml solution) were injected subconjunctivally 180 degrees from the filtering site once daily up to seven times during the first week after surgery. **Examination methods:** NR IOP measured at 1week, 2 weeks, 1 month, 2 months, 6 months and 12 months.	**Mean post-operative IOP (mmHg)**	***6 months:*** **Group 1:** 11.1 ± 4.8 **Group 2:** 14.1 ± 4.9 **p value:** 0.1 (Student's t test) ***12 months:*** **Group 1:** 11.6 ± 4.2 **Group 2:** 14.3 ± 3.7 **p value:** 0.1 (Student's t test)	**Funding:** NR **Limitations:** • Randomisation method not clear • Surgeon and patients unblinded • Examination methods NR • Small sample size • Inclusion/exclusion criteria for patients enrolment NR **Additional outcomes:** Visual acuity at 12 months was stable within 1 line of baseline in all eyes in both groups. Mean change in IOP rate at 12 months was 53.4% ± 20.3% with MMC and 43.4% ± 21.3% with 5-FU **Notes:**
			Mean change in IOP from baseline at postoperative measurement	***6 months:*** **Group 1:** 12.9 ± NR **Group 2:** 11.6 ± NR **p value:** NR ***12 months:*** **Group 1:** 12.4 ± NR **Group 2:** 11.4 ± NR **p value:** NR	
			Number of patients with acceptable IOP (<20 mmHg without medications) at 12 months	**Group 1:** 8/10 **Group 2:** 7/10 **p value:** 1 (Fisher's exact calculated by NCC-AC)	
			Number of patients with unacceptable IOP > 20 mmHg at 12 months	**Group 1:** 2/10 **Group 2:** 3/10	
			Corneal epithelial defect	**Group 1:** 0/10 **Group 2:** 3/10 **p value:** 0.2 (Fisher's exact calculated by NCC-AC)	
			Wound leakage	**Group 1:** 2/10 **Group 2:** 2/10 **p value:** 0.6 (Fisher's exact calculated by NCC-AC)	
			Shallow anterior chamber	**Group 1:** 1/10 **Group 2:** 1/10	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
				p value: 1 (Fisher's exact calculated by NCC-AC)	
			Hypotony (IOP between 4 and 6 mmHg)	**Group 1:** 0/10 **Group 2:** 1/10 **p value:** 1 (Fisher's exact calculated by NCC-AC)	

Abbreviations: NR=not reported, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, Sig=<0.05, IOP=intra-ocular pressure, POAG=primary open-angle glaucoma, MMC=mitomycin, 5-FU=5-Fluorouracil

Evidence Table 19 Viscocanalostomy vs. deep sclerectomy

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Egrilmez et al, 2004[40] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG **Setting:** single setting - Turkey **Inclusion criteria:** • POAG + Pigmentary glaucoma (PG) + Pseudoexfoliation glaucoma (PXF) • Uncontrolled IOP on maximal medical therapy **Exclusion criteria:** • Previous intraocular surgery • <21 years **<u>All patients</u>** **N:** 34 (34 eyes) randomised **Age (mean):** 61.7 ± 10.9 **M/F:** 21/13 **Mean IOP:** NR **Drop outs:** 4 (2 drop outs and 2 due to cataract surgery) **POAG:** 20 **PG:** 3 **PXF:** 7 **White:** 30 **<u>Group 1</u>** **N:** 12 **Age (mean):** 60.35 ± 12.96 **M/F:** NR **Mean IOP:** 31.09 ± 12.53 **Drop outs:** 1 **<u>Group 2</u>**	**Group 1** Trabeculectomy (Cairns) **Group 2** NDPS + T-flux non-absorbable implant **Group 3** Viscocanalostomy **Examination methods:** Baseline examinations included visual acuity, Humphrey VF measurement, biomicroscopy, gonioscopy, Goldmann tonometry, autokeratorefreactometry and corneal topography. Measurements of astigmatism, IOP and visual acuity at 1 day, 1 month, 3 months and 6 months Antimetabolites were not used	**Mean IOP ± SD at 6 months** **Mean change in IOP from baseline at 6 months**	**Group 1:** 15.09 ± 3.36 (n=11) **Group 2:** 14.13 ± 2.85 (n=8) **Group 3:** 17.28 ± 3.44 (n=8) **p value:** 0.103 Kruskal-Wallis test **Group 1:** 16.0 ± 11.23* **Group 2:** 11.91 ± 9.19* **Group 3:** 10.08 ± 3.92* **p value:** NR	**Funding:** NR (requested info from author but no response) **Limitations:** • Randomisation method was not clear • Allocation concealment was not reported • Masking of outcome assessment was not reported • No adverse events reported • IOP control is not the primary outcome **Additional outcomes:** Visual acuity Induced astigmatism **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 10 **Age (mean):** 61.25 ± 10.67 **M/F:** NR **Mean IOP:** 27.00 ± 5.35 **Drop outs:** 2 (1 lost to follow up after 1 month and 1 cataract surgery) **<u>Group 3</u>** **N:** 12 **Age (mean):** 63.36 ± 9.68 **M/F:** NR **Mean IOP:** 27.36 ± 11.26 **Drop outs:** 1				intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Evidence Table 20 Non-penetrating surgery vs. trabeculectomy

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Carassa et al., 2003[19] **Study design:** RCT Single-blind Surgeon was masked to treatment allocation **Evidence level:** 1+ **Duration of follow-up:** 24 months	**Patient group:** COAG (POAG + Pseudoexfoliative glaucoma (PXF) **Setting:** single centre - Italy **Inclusion criteria:** • POAG or PXF • Uncontrolled IOP > 21 mmHg on maximal medical therapy or IOP ≤ 21 mmHg with intolerance to current medications or poor compliance • ≥ 45 years **Exclusion criteria:** • Other ocular disease including congenital glaucoma or angle closure glaucoma • Previous ocular surgery • Abnormality preventing reliable tonometry **<u>All patients</u>** **N:** 50 (50 eyes) **Age (mean):** NR **M/F:** 20/30 **Mean IOP:** NR **Drop outs:** 1 **<u>Group 1</u>** **N:** 25 eyes **Age (mean ± SD):** 68 ± 10.5 **M/F:** 10/15 **Mean ± SD IOP:** 22.88 ± 7.18	**Group 1** Trabeculectomy + 5FU ** **Group 2** Viscocanalostomy (Stegmann) **Examination methods:** Baseline IOP measured using slit lamp mounted applanation tonometer. Postoperative visits at 1 day, 1 week, 1, 2, 3 months and every months thereafter	**Mean IOP ± SD at 6 months**	**Group 1:** 12.76 ± 2.44 **Group 2:** 16.46 ± 4.96 **p value:**	**Funding:** Self funded (confirmed by author) **Limitations:** • Randomisation method was not reported • Masking of outcome assessment was not reported • Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Additional outcomes:** • Ocular discomfort score at 12 months • Reduction in visual acuity at end point **Notes:** **9 eyes received postoperative 5-FU injections and 2 eyes received argon laser suture lysis but these were allowed in treatment protocol and not considered as a treatment failure For group 2, any further intervention was
			Mean IOP ± SD reduction at 6 months	**Group 1:** 10.12 ± 6.32* **Group 2:** 8.29 ± 4.81*	
			Mean IOP ± SD at 12 months	**Group 1:** 13.04 ± 3.08 (n=25) **Group 2:** 16.38 ± 5.05 (n=24) **p value:** 0.01 (unpaired t-test) **signif.** *p = 0.0074 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean IOP ± SD reduction at 12 months	**Group 1:** 9.84 ± 6.24* **Group 2:** 8.37 ± 4.82*	
			Mean IOP ± SD at 24 months	**Group 1:** 14.04 ± 4.64 (n=25) **Group 2:** 16.29 ± 5.10 (n=24) **p value:** 0.11 (unpaired t-test) *p = 0.12 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean change in IOP from baseline at 24 months	**Group 1:** 8.76 ± NR **Group 2:** 8.46 ± NR **p value:** NR	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications) at 12 months	**Group 1:** 80% (n=20) (22/25) **Group 2:** 76% (n=19) (19/25) **p value:** 0.6 (log rank test)	
			Kaplan-Meier cumulative % Failure to control IOP without medications at 12 months	**Group 1:** 3/25 **Group 2:** 6/25	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Visual acuity: 0.42 ± 0.3 **White:** 25 **Preoperative medications:** 3.06 (range 2-5) **POAG:** 22 **PXF:** 3 **Drop outs:** 0 **<u>Group 2</u>** **N:** 25 eyes **Age (mean ± SD):** 67.4 ± 15.8 **M/F:** 10/15 **Mean ± SD IOP:** 24.75 ± 6.73 **Visual acuity:** 0.56 ± 0.34 **White:** 25 **Preoperative medications:** 3.12 (range 2-5) **POAG:** 24 **PXF:** 1 **Drop outs:** 1 eye converted to trab but considered as withdrawal		**Kaplan-Meier cumulative % probability of IOP success (<16 mmHg without medications) at 24 months**	**Group 1:** 72% (n=18) **Group 2:** 56% (n=14) **p value:** 0.17 (log rank test)	considered a failure. * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.
			Number of eyes requiring re-operation (treatment failure)**	**Group 1:** 0/25 **Group 2:** 4/25 **p value:** NR *p = 0.12 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			Number of eyes requiring additional medications (treatment failure)**	**Group 1:** 5/25 **Group 2:** 2/25 **p value:** NR *p = 0.42 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			Hyphaema (1-2 mm)	**Group 1:** 1/25 (4%) **Group 2:** 3/24 (12.5%)	
			Hypotony	**Group 1:** 5/25 (20%) **Group 2:** 0/24 (0%)	
			Choroidals	**Group 1:** 1/25 (4%) **Group 2:** 0/25 (0%)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Chiselita, 2001[20] **Study design:** RCT Single Blind **Evidence level:** 1+ **Duration of follow-up:** 18 months	**Patient group:** POAG **Setting:** single centre - Romania **Inclusion criteria:** • Symmetrical POAG with uncontrolled IOP on maximal medical therapy • Both eyes > 23 mmHg on at least 2 medications • > 40 years old **Exclusion criteria:** • Asymmetrical POAG • Secondary OAG • Angle-closure glaucoma • Previous eye surgery • Previous argon laser treatment within 30 days **<u>All patients</u>** **N:** 17 (34 eyes) **Age (mean):** 60.17 ± 7.3 **M/F:** 9/8 **Mean IOP:** NR **Drop outs:** 0 **<u>Group 1</u>** **N:** 17 **Age (mean):** see above **M/F:** see above **Mean IOP:** 27.29 ± 2.08 **Visual Acuity:** 0.47 ± 0.26 **C/D Ratio:** 0.75 ± 0.11 **Drop outs:** 0	**Group 1** Trabeculectomy (Cairns) **Group 2** Non-penetrating Deep Sclerectomy **Examination methods:** ***Preoperative:*** Visual acuity, biomicroscopy, gonioscopy, Goldmann applanation tonometry, Humphrey VF analysis, fundus examination, C/D ratio ***Postoperative:*** Included visual acuity, Humphrey VF analysis, C/D ratio repeated every 3 months. Diurnal IOP curves measured at 1, 2, 3, 6, 12, 18 months. All measurements performed by same physician masked to allocation	**Mean IOP ± SD at 18 months**	**Group 1:** 17.27 ± 1.2 (n=17) **Group 2:** 20.90 ± 4.0 (n=17) **p value:** <0.0015 ANCOVA	**Funding:** NR **Limitations:** • Randomisation method unclear • Allocation concealment not reported • Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Additional outcomes:** Kaplan-Meier cumulative probability for achieving postoperative IOP >30% less than preoperative IOP **Notes:** No antimetabolite use or postoperative goniopuncture. Fellow eyes randomised * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from
			Mean IOP ± SD at 6 months	**Group 1:** 16.41 ± 1.8 **Group 2:** 19.17 ± 3.6	
			Mean change in IOP from baseline at 6 months	**Group 1:** 10.88 ± 1.96* **Group 2:** 8.53 ± 2.40*	
			Mean IOP ± SD at 12 months	**Group 1:** 16.78 ± 1.6 **Group 2:** 20.35 ± 4.5	
			Mean change in IOP from baseline at 12 months	**Group 1:** 10.51 ± 2.56* **Group 2:** 7.35 ± 3.35*	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications) at 12 months	**Group 1:** 92.59% (16/17) **Group 2:** 44.57% (8/17) **p value:** 0.00034 (Cox's F Test) **signif.**	
			Kaplan-Meier cumulative % probability number of eyes with unacceptable IOP without medications at 12 months	**Group 1:** 1/17 **Group 2:** 9/17 **p value:**	
			Number requiring postoperative medications	**Group 1:** 6/17 **Group 2:** 9/17 **p value:** Not signif.	
			Hyphaema	**Group 1:** 7/17 **Group 2:** 0/17 **p value:** 0.003 (Chi-squared)	
			Inflammation	**Group 1:** 2/17 **Group 2:** 0/17	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 17 **Age (mean):** see above **M/F:** see above **Mean IOP:** 27.70 ± 2.22 **Visual Acuity:** 0.48 ± 0.23 **C/D Ratio:** 0.75 ± 0.12 **Drop outs:** 0			**p value:** not signif. (Chi-squared)	baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook.
			Cataract	**Group 1:** 4/17 **Group 2:** 0/17 **p value:** 0.0279 (Chi-squared)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cillino et al., 2005[22] & Cillino et al., 2008[21] **Study design:** RCT Single Blind **Evidence level:** 1+ Single blind **Duration of follow-up:** 12 months	**Patient group:** POAG and pseudoexfoliative glaucoma (PXF) **Setting:** single centre - Itlay **Inclusion criteria:** • IOP > 21 mmHg on maximal medications • Visual field deterioration **Exclusion criteria:** • Cataract • Other ocular diseases • Previous eye surgery **<u>All patients</u>** **N:** 40 (40 eyes) **Age (mean):** NR **M/F:** 20/20 **Mean IOP:** NR **Drop outs:** 3 **<u>Group 1</u>** **N:** 21 **Age (mean):** 68.9 ± 6.4 **M/F:** 10/11 **Mean IOP:** 28.0 ± 6.0 **POAG:** 15 **PXF:** 6 **Drop outs:** 0 **<u>Group 2</u>** **N:** 22 **Age (mean):** 71.9 ± 7.1 **M/F:** 10/9	**Group 1** Punch Trabeculectomy (Crozafon-De Laage) + Mitomycin C (MMC) 0.2 mg/ml for 2 minutes **Group 2** Non-penetrating Deep Sclerectomy (DS) + Mitomycin C (MMC) 0.2 mg/ml for 2 minutes **Examination methods:** ***Preoperative:*** Goldmann applanation tonometry, Humphrey VF analysis, slit lamp examination ***Postoperative:*** IOP measured at each visit at 1 day, 1, 2, 3 weeks, 1, 3, 6, 9 & 12 months. Investigators were blinded	**Mean IOP ± SD at 6 months**	**Group 1:** 13.8 ± 4.0 **Group 2:** 14.4 ± 2.6 **p value:** 0.78 ANOVA	**Funding:** NR **Limitations:** • Allocation concealment not reported **Additional outcomes:** **Notes:** Author confirms use of computer to generate randomisation sequence NdYAG: goniopuncture was performed in 4/19 eyes in the DS group * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. **A paper with longer term data was published by the same
			Mean change in IOP from baseline at 6 months	**Group 1:** 14.2 ± 5.29* **Group 2:** 15.2 ± 4.39*	
			Mean IOP ± SD at 12 months	**Group 1:** 16.1 ± 3.8 (n=21) **Group 2:** 14.5 ± 4.0 (n=19) **p value:** 0.53 ANOVA	
			Mean change in IOP from baseline at 12 months	**Group 1:** 11.9 ± 6.94* **Group 2:** 15.1 ± 4.14* **p value:** NR	
			Mean IOP ± SD at 24 months**	**Group 1:** 16.9 ± 2.4 **Group 2:** 16.8 ± 3.4 **p value:** 0.99 ANOVA	
			Mean IOP ± SD at 48 months**	**Group 1:** 17.8 ± 3.6 **Group 2:** 17.6 ± 3.4 **p value:** 0.97 ANOVA	
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	**Group 1:** 15/21 (71%) **Group 2:** 15/19 (79%) **p value:** 0.72 (Fishers exact test)	
			Number of eyes with acceptable IOP (<17 mmHg without medications at 12 months	**Group 1:** 13/21 (62%) **Group 2:** 12/19 (63%) **p value:** 0.81 (Fishers exact test)	
			Failure to control IOP without medications at 12 months	**Group 1:** 6/21 **Group 2:** 3/19	
			Hypotony (<5 mmHg for > 2 weeks)	**Group 1:** 8/21 **Group 2:** 0/19 **p value:** 0.003 (Fishers exact test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Mean IOP: 29.6 ± 5.8 **POAG:** 12 **PXF:** 7 **Drop outs:** 3			**signif**	author in 2008[21]. The outcome data have been reported in this evidence table but they do not affect the main outcome data reported at 12 months.
			Hyphaema	**Group 1:** 9/21 **Group 2:** 4/19 **p value:** 0.26 (Fishers exact test)	
			Inflammation	**Group 1:** 4/21 **Group 2:** 1/19 **p value:** 0.49(Fishers exact test)	
			Flat anterior chamber	**Group 1:** 2/21 **Group 2:** 0/19 **p value:** 0.046 (Fishers exact test)	
			Shallow anterior chamber	**Group 1:** 7/21 **Group 2:** 1/19 **p value:** 0.046 (Fishers exact test)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Egrilmez et al, 2004[40] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** COAG **Setting:** single setting - Turkey **Inclusion criteria:** • POAG + Pigmentary glaucoma (PG) + Pseudoexfoliative glaucoma (PXF) • Uncontrolled IOP on maximal medical therapy **Exclusion criteria:** • Previous intraocular surgery • <21 years **All patients** **N:** 34 (34 eyes) randomised **Age (mean):** 61.7 ± 10.9 **M/F:** 21/13 **Mean IOP:** NR **Drop outs:** 4 (2 drop outs and 2 due to cataract surgery) **POAG**: 20 **PG**: 3 **PXF**: 7 **White**: 30 **Group 1** **N:** 12 **Age (mean):** 60.35 ± 12.96 **M/F:** NR **Mean IOP:** 31.09 ± 12.53 **Drop outs:** 1 **Group 2** **N:** 10	**Group 1** Trabeculectomy (Cairns) **Group 2** NDPS + T-flux non-absorbable implant **Group 3** Viscocanalostomy **Examination methods:** Baseline examinations included visual acuity, Humphrey VF measurement, biomicroscopy, gonioscopy, Goldmann tonometry, autokeratorefreactometry and corneal topography. Measurements of astigmatism, IOP and visual acuity at 1 day, 1 month, 3 months and 6 months Antimetabolites were not used	**Mean IOP ± SD at 6 months** **Mean change in IOP from baseline at 6 months**	**Group 1:** 15.09 ± 3.36 (n=11) **Group 2:** 14.13 ± 2.85 (n=8) **Group 3:** 17.28 ± 3.44 (n=8) **p value:** 0.103 Kruskal-Wallis test **Group 1:** 16.0 ± 11.23* **Group 2:** 11.91 ± 9.19* **Group 3:** 10.08 ± 3.92* **p value:** NR	**Funding:** NR (requested info from author but no response) **Limitations:** • Randomisation method was not clear • Allocation concealment was not reported • Masking of outcome assessment was not reported • No adverse events reported • IOP control is not the primary outcome **Additional outcomes:** Visual acuity Induced astigmatism **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Age (mean): 61.25 ± 10.67 **M/F:** NR **Mean IOP:** 27.00 ± 5.35 **Drop outs:** 2 (1 lost to follow up after 1 month and 1 cataract surgery) **<u>Group 3</u>** **N:** 12 **Age (mean):** 63.36 ± 9.68 **M/F:** NR **Mean IOP:** 27.36 ± 11.26 **Drop outs:** 1				similar enough to viscocanalostomy to produce an equivalent effect size.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
El Sayyad et al., 2000[41] **Study design:** RCT **Evidence level:** 1 + **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** single centre – Saudi Arabia **Inclusion criteria:** • Symmetrical POAG with uncontrolled IOP > 21 mmHg on maximal medical therapy • > 35 years old **Exclusion criteria:** • Previous eye surgery • Patients with significant posterior segment eye disorders **<u>All patients</u>** **N:** 39 (78 eyes) **Age (mean):** 53.4 ± 9.6 **M/F:** 24/15 **Mean IOP:** NR **Drop outs:** 0 (patients failing sclerectomy procedure were replaced) **<u>Group 1</u>** **N:** 39 **Age (mean):** see above **M/F:** see above **Mean IOP:** 28.2 ± 4.7 **Pre-op glaucoma meds:** 2.6 ± 0.6 **Drop outs:** 0 **<u>Group 2</u>** **N:** 39 **Age (mean):** see above	**Group 1** Trabeculectomy **Group 2** Non-penetrating Deep Sclerectomy **Examination methods:** ***Preoperative:*** Visual Acuity, applanation tonometry, slit lamp examination & ophthalmoscopy ***Postoperative:*** Details of examinations not reported but measurements taken at 1 day, 1 week, 1 month then at 3, 6, 9 and 12 months	**Mean IOP ± SD at 6 months**	**Group 1:** 13.7 ± 5.4 (n=39) **Group 2:** 14.9 ± 4.3 (n=39) **p value:** 0.28 (unpaired t test)	**Funding:** NR **Limitations:** • Randomisation method was not clear • Allocation concealment was not reported • Masking of outcome assessment was not reported **Additional outcomes:** Postoperative glaucoma meds at 12 months **Group 1:** 0.27 ± 0.5 **Group 2:** 0.30 S 0.4 Visual Acuity (Snellen lines) at 12 months No significant difference **Notes:** Fellow eyes randomised Goniopuncture with Nd:YAG laser was performed in 4/39 eyes in NPDS group and Argon laser suture lysis was performed in 17/39 eyes in trabeculectomy group. 5-FU was used
			Mean change in IOP from baseline at 6 months	**Group 1:** 14.5 ± 5.1 **Group 2:** 13.2 ± 4.2 **p value:** 0.16 (unpaired t test)	
			Mean IOP ± SD at 12 months	**Group 1:** 14.1 ± 4.6 (n=39) **Group 2:** 15.6 ± 4.2 (n=39) **p value:** 0.13 (unpaired t test)	
			Mean change in IOP from baseline at 12 months	**Group 1:** 14.1 ± 6.4 **Group 2:** 12.3 ± 4.2 **p value:** 0.15 (unpaired t test)	
			Number of eyes with acceptable IOP (<21 mmHg without medications at 12 months	**Group 1:** 33/39 (85%) **Group 2:** 31/39 (79%) **p value:** 0.55 (Chi squared)	
			Failure to control IOP <21 mmHg without medications	**Group 1:** 6/39 **Group 2:** 8/39	
			Hyphaema	**Group 1:** 3/39 **Group 2:** 1/39 **p value:** 0.6 (Chi-squared)	
			Hypotony	**Group 1:** 1/39 **Group 2:** 0/39 **p value:** 0.9 (Chi-squared)	
			Intensive Uveitis	**Group 1:** 2/39 **Group 2:** 0/39 **p value:** 0.47 (Chi-squared)	
			Cataract	**Group 1:** 1/39 **Group 2:** 0/39 **p value:** 0.9 (Chi-squared)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	M/F: see above **Mean IOP:** 27.9 ± 5.9 **Pre-op glaucoma meds:** 2.4 ± 0.7 **Drop outs:** 0				postoperatively 17/39 eyes of the NPDS group and 15/39 in the trabeculectomy group

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Jonescu-Cuypers et al., 2001[67] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 6 months	**Patient group:** POAG (all white patients) **Setting:** single centre - Germany **Inclusion criteria:** • Uncontrolled high tension glaucoma on maximal medications • IOP > 30 mmHg with or without medication • Glaucomatous damage defined by VF loss or progressive cupping **Exclusion criteria:** • Those with previous ocular surgery • Legally blind fellow eye • Corneal abnormalities preventing applanation tonometry **<u>All patients</u>** **N:** 20 patients (20 eyes) **Age (mean):** 62.5 ± 13.1 **M/F:** 11/9 **Mean IOP:** 29.65 ± 6.45 **Drop outs:** 0 **All white patients** **<u>Group 1</u>** **N:** 10 **Age (mean):** NR **M/F:** NR **Mean IOP:** 28.1 ± 5.84 **C/D ratio:** 0.67 ± 0.26 **Drop outs:** 0 **<u>Group 2</u>**	**Group 1** Trabeculectomy (Cairns modification) **Group 2** Viscocanalostomy (Stegmann)** **Examination methods:** ***Preoperative*** IOP measurement, visual acuity, gonioscopy, slit lamp biomicroscopy, indirect ophthalmoscopy of the retina, biomorphometry of papilla by laser scanning, VF testing with Humphrey and ultrasonography for scleral thickness. ***Postoperative*** IOP measurement, biomorphometry of papilla by laser scanning, VF testing with Humphrey. Examinations monthly for 6-8 months after surgery **2/10 in the viscocanalostomy group had trabeculectomies with mitomycin C and 1/10 in same group had a sclerectomy due to IOP spikes	**Mean postoperative IOP ± SD - Follow-up time not specified**	**Group 1:** 15.6 ± 3.17 (n=10) **Group 2:** 18.3 ± 5.03 (n=10) **p value:** NR *p = 0.17 2-sided t-test with equal variances calculated by NCC-AC as ITT (n=10 in both groups)*	**Funding:** NR (emailed author) **Limitations:** • Randomisation method not clear • Outcome assessment was not masked **Additional outcomes:** **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.
			Mean change in IOP from baseline mean follow up of 6 months (range 6-8 months)	**Group 1:** 12.5 ± 5.06* **Group 2:** 12.29 ± 4.97* **p value:**	
			Number of eyes with acceptable IOP (<20 mmHg without medications or need for re-operation) at follow up of 6 months (range 6-8 months)	**Group 1:** 5/10 (50%) **Group 2:** 0/10 (0%) **p value:** NR *p = 0.03 2-sided Fishers exact test calculated by NCC-AC as ITT (n=10 in both groups)*	
			Failure to control IOP without medications or a need for further surgery at follow up of 6 months (range 6-8 months)	**Group 1:** 5/10 (50%) **Group 2:** 10/10 (100%)	
			Bleeding into conjunctiva	**Group 1:** 0/10 **Group 2:** 1/10 **p value:** NR	
			Leaking Bleb	**Group 1:** 1/10 **Group 2:** 0/10 **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	N: 10 **Age (mean):** NR **M/F:** NR **Mean IOP:** 31.2 ± 6.96 **C/D ratio:** 0.85 ± 0.13 **Drop outs:**				

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kobayashi et al., 2003[77] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG **Setting:** single setting - Japan **Inclusion criteria:** • IOP ≥ 22mmHg on maximal medical therapy **Exclusion criteria:** • Angle-closure, post-traumatic, uveitic, neovascular or dysgenetic glaucoma • Patients needing combined cataract procedures **<u>All patients</u>** **N:** 25 (50 eyes) **Age (mean):** 62..5 ± 7.4 **M/F:** 11/14 **Mean IOP:** NR **Drop outs:** 0/25 **<u>Group 1</u>** **N:** 25 eyes **Age (mean):** see above **M/F:** see above **Mean IOP:** 24.8 ± 2.6 **VF Mean Deviation:** -12.81 ± 5.6 **Drop outs:** 0 **<u>Group 2</u>** **N:** 25 eyes **Age (mean):** see above **M/F:** see above **Mean IOP:** 25.0 ± 2.2	**Group 1** Trabeculectomy (Cairns) with 0.04% MMC sponges after dissection Laser suture lysis was performed if bleb was flat or target IOP not reached **Group 2** Viscocanalostomy (Stegmann) Goniopuncture with Nd:YAG laser performed after if target pressure not reached **Examination methods:** ***Baseline examinations:*** Humphrey VF test, gonioscopy, scanning laser tomography. IOP measured at 3 visits in 2 week period prior to study and 3 measurements averaged. ***Postoperative examinations:*** Patients reviewed at 1, 3 days, 1, 2 weeks and 1, 2, 3, 4, 5, 6, 9, 12 months after surgery.	**Mean IOP ± SD at 6 months**	**Group 1:** 11.8 ± 4.6 (n=25) **Group 2:** 16.9 ± 2.8(n=25) **p value:** <0.0001 student t-test	**Funding:** Self-funded. **Limitations:** • Allocation concealment was not reported • Masking of outcome assessment was not reported **Additional outcomes:** VF change as Mean Deviation at 12 months **Group 1**: -0.30 ± 0.85 **Group 2**: -0.21 ± 0.28 Change in visual acuity at 12 months **Notes:** Eyes randomised. Patient received viscocanalostomy in 1 eye and trabeculectomy in the fellow eye. "nd procedure was performed 1-2 weeks after the first. 14/25 (56%) viscocanalostomy eyes received goniopuncture with Nd:YAG laser post surgery.
			Mean change in IOP from baseline at 6 months	**Group 1:** 13.0 ± 5.4 **Group 2:** 8.1 ± 3.5 **p value:** <0.0001 student t-test **signif.** *p = 0.0005 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean IOP ± SD at 12 months	**Group 1:** 12.6 ± 4.3 (n=25) **Group 2:** 17.1 ± 1.5 (n=25) **p value:** <0.0001 student t-test	
			Mean change in IOP from baseline at 12 months	**Group 1:** 12.3 ± 5.2 **Group 2:** 7.8 ± 3.1 **p value:** <0.0001 student t-test **signif.** *p = 0.0006 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Number of eyes with acceptable IOP (<20 mmHg & change in IOP or >30% without medications) at 12 months	**Group 1:** 22/25 (88%) **Group 2:** 15/25 (60%) **p value:** 0.024 (Chi-squared) *p = 0.051 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			IOP < 16 mmHg without medication at 12 months	**Group 1:** 20/25 (80%) **Group 2:** 10/25 (40%) **p value:** 0.0039 (Chi-squared) *p = 0.009 2-sided Fishers exact test calculated by NCC-AC as ITT (n=25 in both groups)*	
			Failure to control IOP without medications or a need for further surgery at 12 months	**Group 1:** 3/25 **Group 2:** 10/25	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	VF Mean Deviation: -13.72 ± 4.97 **Drop outs:** 0	3 IOP measurements taken in each eye and mean used. Optic nerve was examined with Goldmann lens and tomography performed at 1 year interval. V F measured at 6 months and 12 months.	**Complete failure defined by need for further surgery or loss of Visual Function**	**Group 1:** 0/25 **Group 2:** 1/25 **p value:** Not signif.	
			Hypotony	**Group 1:** 5/25 (20%) **Group 2:** 0/25 **p value:** 0.0184 (Chi-squared).	
			Hypaema	**Group 1:** 4/25 (16%) **Group 2:** 0/25 **p value:** 0.0371	
			Failed Bleb	**Group 1:** 2/25 (8%) **Group 2:** NR **p value:** NR	
			Bleb Formation	**Group 1:** NR **Group 2:** 5/25 **p value:** NR	
			Cataract formation	**Group 1:** 2/25 **Group 2:** 0/25 **p value:** Not signif.	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Luke et al., 2002[90] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG, pseudoexfoliative glaucoma (PXF) & pigmentary glaucoma (PG) **Setting:** single centre - Germany **Inclusion criteria** • Uncontrolled IOP on maximal medications • >21 years old **Exclusion criteria:** • Previous ocular surgery **<u>All patients</u>** **N:** 60 (60 eyes) **Age (mean):** 61.4 ± 17.6 **M/F:** 57/31 **Mean IOP:** 27.1 ± 7.1 **Drop outs:** 0 **POAG:** 33 **PXF:** 20 **PG:** 7 **<u>Group 1</u>** **N:** 30 **Age (mean):** NR **M/F:** NR **Mean IOP:** 26.9 ± 7.4 **Drop outs:** 0 **Number of Medications:** 2.5 ± 1.1 **<u>Group 2</u>** **N:** 30 **Age (mean):** NR **M/F:** NR **Mean IOP:** 27.2 ± 6.9	**Group 1** Trabeculectomy (Cairns) **Group 2** Viscocanalostomy **Examination methods:** ***Preoperative:*** Visual acuity, VF examination using Humphrey, biomicroscopy, gonioscopy, Goldmann applanation tonometry ***Postoperative:*** Visual acuity, VF examination using Humphrey, biomicroscopy, gonioscopy, Goldmann applanation tonometry performed daily for 1 week, then at 1, 6, 12 months Laser suture lysis was performed on 11/30 eyes in trabeculectomy group if IOP was uncontrolled	**Mean IOP ± SD at 6 months**	**Group 1:** 15.5 ± 3.0 **Group 2:** 16.0 ± 4.1 **p value:** 0.15 student t-test	**Funding:** Not reported **Limitations:** • Randomisation method is unclear • Allocation concealment was not reported • Masking of outcome assessment was not reported • Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Additional outcomes:** **Notes:** *As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter
			Mean change in IOP from baseline at 6 months	**Group 1:** 16.78 ± 6.45* **Group 2:** 11.2 ± 4.98* **p value:** NR	
			Mean IOP ± SD at 12 months	**Group 1:** 15.0 ± 3.5 **Group 2:** 17.1 ± 5.4 **p value:** 0.15 student t-test	
			Mean change in IOP from baseline at 12 months	**Group 1:** 11.9 ± 6.41* **Group 2:** 10.1 ± 3.87* **p value:** NR	
			Kaplan-Meier cumulative % probability of IOP success (<22 mmHg without medications) at 12 months	**Group 1:** 56.7% (n=30) (17/30) **Group 2:** 30% (n=30) (9/30) **p value:** 0.041 (log rank test) **signif.**	
			Kaplan-Meier cumulative % probability of number of eyes with unacceptable IOP without medications or a need for further surgery at 12 months	**Group 1:** 13/30 **Group 2:** 21/30	
			Hyphaema	**Group 1:** 8/30 (26.7%) **Group 2:** 3/30 (10%) **p value:** 0.095 (Chi-squared)	
			Hypotony (<6 mmHg)	**Group 1:** 11/30 (36.7%) **Group 2:** 6/30 (20%) **p value:** 0.152 (Chi-squared)	
			Cataract Progression	**Group 1:** 2/30 (6.7%) **Group 2:** 0/30 **p value:** 0.15 (Chi-squared)	
			Bleb formation	**Group 1:** 30/30 **Group 2:** 17/30	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 0 **Number of Medications:** 2.9 ± 0.9			**p value:** <0.001 (Chi-squared)	intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Yalvac et al., 2004[163] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 36 months (mean follow up 18 months range 6-38)	**Patient group:** POAG **Setting:** single centre - Turkey **Inclusion criteria:** • Uncontrolled POAG on maximal medical therapy **Exclusion criteria:** • Congenital glaucoma, angle closure glaucoma, neovascular glaucoma, traumatic glaucoma & uveitic glaucoma • Previous ocular surgery **<u>All patients</u>** **N:** 50 (50 eyes) **Age (mean):** NR **M/F:** 36/14 **Mean IOP:** NR **Drop outs:** 0 **<u>Group 1</u>** **N:** 25 eyes **Age (mean ± SD):** 66.8 ± 10.2 **M/F:** 19/6 **Mean ± SD IOP:** 37.7 ± 9.0 **Preoperative medications:**: 3 (range 2-4) **Drop outs:** 0 **<u>Group 2</u>** **N:** 25 eyes **Age (mean ± SD):** 63.6 ± 12.6 **M/F:** 17/8	**Group 1** Trabeculectomy (Cairns) **Group 2** Viscocanalostomy (similar to Stegmann) **Examination methods:** ***Preoperative:*** IOP measurement by applanation tonometry, visual acuity, gonioscopy, slit lamp biomiscroscopy, indirect ophthalmoscopy of the optic nerve, VF examination using Humphrey 24-2. ***Postoperative:*** IOP measurement by Goldmann applanation tonometry, visual acuity, gonioscopy, slit lamp biomiscroscopy, fundoscopy Patients were examined at 1 day, 1 week, 1, 3 & 6 months, 1, 2 & 3 years. No antimetabolites were used	**Mean IOP ± SD at 6 months**	**Group 1:** 16.0 ± 5.3 (n=25) **Group 2:** 18.1 ± 5.2 (n=25) **p value:** 0.206 (unpaired t-test) *p = 0.16 2-sided t-test with equal variances calculated by NCC-AC as ITT (n=25 in both groups)*	**Funding:** NR (requested info from author but no response) **Limitations:** • Randomisation method was not clear • Allocation concealment not reported • Masking of outcome assessment was not reported • Binary outcomes for IOP Success/Failure estimated from Kaplan-Meier curve **Notes:** * As standard deviations for the change in IOP from baseline were not reported they were imputed using correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep
			Mean change in IOP from baseline at 6 months	**Group 1:** 24.1 ± 7.84* (n=25) **Group 2:** 15.7 ± 5.73* (n=25)	
			Mean IOP ± SD at 12 months	**Group 1:** 16.3 ± 3.9 (n=25) **Group 2:** 20.3 ± 5.6 (n=25) **p value:** 0.027 (unpaired t-test) **signif.** *p = 0.005 2-sided t-test with equal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean change in IOP from baseline at 12 months	**Group 1:** 24.1 ± 7.82* (n=25) **Group 2:** 15.7 ± 5.71* (n=25)	
			Mean IOP ± SD at 24 months	**Group 1:** 18.6 ± 4.3 (n=25) **Group 2:** 21.6 ± 10.8 (n=25) **p value:** 0.43 (unpaired t-test) *p = 0.21 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Mean IOP ± SD at 36 months	**Group 1:** 16.0 ± 7.1 (n=25) **Group 2:** 17.8 ± 4.6 (n=25) **p value:** 0.69 (unpaired t-test) *p = 0.29 2-sided t-test with unequal variances calculated by NCC-AC as ITT (n=25 in both groups)*	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications)	**Group 1:** 17/25 66.2% **Group 2:** 13/25 52.9% **p value:** 0.311 (log rank test)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Mean ± SD IOP: 36.0 ± 8.0 **Preoperative medications:** 3.1 (range 2-4) **Drop outs:** 0		**at 6 months**		sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size. **Additional outcomes:** Visual acuity change
			Kaplan-Meier cumulative % probability of number of eyes with unacceptable IOP without medications or need for further surgery at 6 months	**Group 1:** 8/25 **Group 2:** 12/25	
			Kaplan-Meier cumulative % probability of IOP success (<21 mmHg without medications) at 3 years	**Group 1:** 14/25 55.1% **Group 2:** 9/25 35.3% **p value:** 0.228 (log rank test)	
			Number of eyes requiring additional medications postoperatively	**Group 1:** 10/25 (40%) **Group 2:** 13/25 (52%) *p = 0.40 2-sided Fishers calculated by NCC-AC as ITT (n=25 in both groups)*	
			Transient early Hypotony IOP < 5 mmHg	**Group 1:** 7/25 (28%) **Group 2:** 1/25 (4%) **p value:** 0.002 (Chi-squared) **signif.** *p = 0.049 2-sided Fishers calculated by NCC-AC as ITT (n=25 in both groups)*	
			Hyphaema	**Group 1:** 2/25 (8%) **Group 2:** 1/25 (4%)	
			Bleb encapsulation	**Group 1:** 3/25 (12%) **Group 2:** 1/25 (4%)	
			Cataract	**Group 1:** 7/25 (28%) **Group 2:** 2/25 (8%) **p value:** 0.002 (Chi-squared) **signif.** *p = 0.14 2-sided Fishers calculated by NCC-AC as ITT (n=25 in both groups)*	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Non-penetrating surgery vs. trabeculectomy (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Yarangumeli et al., 2005[164] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** 12 months	**Patient group:** POAG, chronic angle closure glaucoma (CACG) and pseudoexfoliative glaucoma (PXF) **Setting:** single centre - Turkey **Inclusion criteria:** • Uncontrolled high tension glaucoma on maximal medications **Exclusion criteria:** • High risk patients requiring antimetabolites such as those with previous ocular surgery • Secondary or developmental glaucoma • < 40 years old • History of ocular inflammation or trauma **All patients** **N:** 22 (44 eyes) **Age (mean):** 64.3 ± 10.5 **M/F:** 12/10 **Mean IOP:** NR **Drop outs:** 0 **POAG:** 7 **PXF:** 11 **CACG**: 4 **Group 1** **N:** 22 **Age (mean):** see above **M/F:** see above **Mean IOP:** 39.3 ± 11.9	**Group 1** Trabeculectomy (Cairns/Watson modification) **Group 2** Viscocanalostomy (Stegmann) **Examination methods:** IOP measured by Goldmann tonometry by same observer. Preoperatively and at 1, 2, 4 and 12 weeks postoperatively then every 3 months for 1st year and 6 month intervals thereafter. No antimetabolites in either group	**Mean IOP ± SD at 6 months**	**Group 1:** 9.6 ± 3.8 **Group 2:** 12.6 ± 4.0 **p value:** 0.026 (repeated measures ANOVA)	**Funding:** Self-funded (confirmed by author) **Limitations:** • **4/22 patients had CACG but these were excluded from the Number of patients with unacceptable IOP results • Outcome assessment was not masked **Additional outcomes:** • Diffuse elevated blebs • Thin walled, multi-cystic blebs • Low-lying, localised blebs **Notes:** One eye randomised using coin tossing to first treatment group. Less than 2 months later fellow eye received remaining procedure. Eye to be randomised to 1st treatment was the one with most severe glaucoma, otherwise coin used to select eye. * As standard deviations for the change in IOP from baseline were not reported they were imputed using
			Mean change in IOP from baseline at 6 months	**Group 1:** 29.7 ± 10.53* **Group 2:** 26.0 ± 9.89* **p value:**	
			Mean IOP ± SD at 12 months	**Group 1:** 9.6 ± 3.8 **Group 2:** 12.6 ± 4.0 **p value:** 0.026 (repeated measures ANOVA)	
			Mean change in IOP from baseline at 12 months	**Group 1:** 29.7 ± 10.53* **Group 2:** 26.0 ± 10.41* **p value:**	
			Number of eyes with acceptable IOP (<18 mmHg without medications) at 12 months	**Group 1:** 14/22 (64%) **Group 2:** 13/22 (59%) **p value:** 0.75 (Chi-squared)	
			Number of eyes with unacceptable IOP without medications at 12 months	**Group 1:** 7/18** **Group 2:** 8/18**	
			Hyphaema	**Group 1:** 1/22 **Group 2:** 1/22 **p value:** NR	
			Persistent hypotony	**Group 1:** 2/22 **Group 2:** 1/22 **p value:** NR	
			Cataract progression	**Group 1:** 7/22 **Group 2:** 2/22 **p value:** NR	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Drop outs: 0 **<u>Group 2</u>** **N:** 22 **Age (mean):** see above **M/F:** see above **Mean IOP:** 38.6 ± 12.5 **Drop outs:** 0				correlation coefficients measuring change from baseline for each arm derived from the study El Sayyad 2000[41] using the methods detailed in the Cochrane handbook. Although El Sayyad compares trabeculectomy to deep sclerectomy, the latter intervention was considered similar enough to viscocanalostomy to produce an equivalent effect size.

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Evidence Table 21 Non-penetrating surgery plus augmentation vs. non-penetrating surgery

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Neudorfer et al., 2004[111] **Study design:** RCT **Evidence level:** 1+ **Duration of follow-up:** At least 24 months. Clinical visits that extended longer than 27 months were considered as 2 year postoperative follow ups.	**Patient group:** POAG **Setting:** single centre - Israel **Inclusion criteria:** Open angle glaucoma patients: • IOP ≥ 22 mmHg with maximal medications • Glaucomatous disc cupping • Visual field defect • Open angles on gonioscopy **Exclusion criteria:** • Secondary glaucoma, neovascular or juvenile glaucomas • iridocorneal endothelial syndrome • uveitis **<u>All patients</u>** **N:** 26 (26 eyes) **Age (mean ± SD):** NR **M/F:** 13/13 **Mean IOP:** **Drop outs:** 0 **<u>Group 1</u>** **N:** 13 **Age (mean ± SD):** 65.8 ± 6.8 **M/F:** 5/8 **Mean IOP:** 26.5 ± 2.5 **Drop outs:** 0	**Group 1** Deep Sclerectomy with collagen implant only **Group 2** Deep Sclerectomy with collagen implant + MMC 0.3mg/ml for 3 minutes **Examination methods:** IOP. Best corrected visual acuity for distance based on the results of retinoscopy and manifest refraction.	**Mean preoperative IOP**	**Group 1:** 26.5 ± 2.5 **Group 2:** 31.5 ± 5.7 **p value: significant**	**Funding:** NR **Limitations:** • Mean preoperative IOP significantly higher in the MMC group than in control despite randomisation. • Patients receiving MMC had been taking significantly greater mean number of medications preoperatively. • Study was underpowered to detect a difference between the groups • Randomisation method, allocation concealment and masking of outcome assessment were not reported **Additional outcomes:** **Visual acuity deterioration (>2 lines on the Snellen chart)** Group 1: 0/13 Group 2: 0/13
			Mean IOP at 12 months	**Group 1:** 17.2 ± 3.9 **Group 2:** 15.6 ± 3.5 **p value:** significant baseline-12 months for each group not between groups	
			IOP % difference from baseline to 12 months	**Group 1:** 34.8 ± 15.3 **Group 2:** 47.8 ±18.1 **p value:** not significant between groups	
			Mean IOP at 24 months	**Group 1:** 17.8 ± 2.8 **Group 2:** 15.8 ± 5.6 **p value:** significant baseline-24 months for each group not between groups	
			IOP % difference from baseline to 24 months	**Group 1:** 32.1 ± 12.2 **Group 2:** 48.1 ± 17.2 **p value:** p = 0.01 significant	
			IOP success <21 mmHg without medications	**Group 1:** 5/13 **Group 2:** 4/13 **p value:** not significant	
			Number of patients with unacceptable IOP ≥ 21 mmHg (with or without meds) at 12 months	**Group 1:** 2/13 **Group 2:** 0/13	
			Number of patients with unacceptable IOP ≥ 21 mmHg (with or without meds) at 24 months	**Group 1:** 1/13 **Group 2:** 1/13	
			Mean number of medications at baseline	**Group 1:** 2.9 ± 0.6 **Group 2:** 3.7 ± 0.6 **p value:** p < 0.05 significant	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	Group 2 **N:** 13 **Age (mean ± SD):** 68.1 ± 8 **M/F:** 8/5 **Mean IOP:** 31.5 ± 5.7 **Drop outs:** 0		**Mean number of medications at 12 months**	**Group 1:** 1.3 ± 1.2 **Group 2:** 1.8 ± 1.5 **p value:** significant baseline-12 months for each group not between groups	**Visual acuity deterioration (1 line on the Snellen chart due to cataract formation)** Group 1: 1/13 Group 2: 2/13 **Notes:**
			Mean number of medications at 24 months	**Group 1:** 1.8 ± 0.9 **Group 2:** 2.0 ± 1.5 **p value:** significant baseline- 24 months for each group not between groups	
			Complications at 24 months	**Postoperative Hyphaema** Group 1: 1/13 Group 2: 2/13 **Filtering blebs** Group 1: 2/13 Group 2: 3/13 Neither bleb leak nor hypotony were present in any of the patient groups.	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Evidence Table 22 Service Provision

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Azuara-Blanco et al., 2007[6] **Study design:** Prospective observational Observer masked	**Patient group:** 671 referrals from community optometrists in Grampian, Scotland. **Inclusion criteria:** >18 years **<u>All patients</u>** **N:** 100 (165 randomised, 65 chose not to participate) **Age (mean):** 67 **M/F:** 52/48 **Mean IOP (mmHg):** 26 **Family history:** 24 **Black:** 1 **Glaucoma diagnosis (management decisions **) by consultant** 1. Normal & discharged: **35** 2. Suspect or OHT requiring review: **32** 3. Suspect or OHT requiring treatment: **8** 4. Glaucoma: **23** 5. Glaucoma requiring urgent treatment: **2**	**Group 1:** 3 community optometrists (CO) that had received in-house training by a consultant ophthalmologist and glaucoma specialist as part of glaucoma optometric service. Training included practical sessions, glaucoma clinics, teaching on diagnostic interventions **Group 2:** Junior (trainee) ophthalmologist **Group 3:** Consultant ophthalmologist **Examination methods:** Each CO examined all 671 referrals for: • Visual acuity (Snellen chart) • VF (threshold strategy 24-2 SITA) • Corneal thickness (ultrasound pachymetry) • Slit lamp biomicroscopy to assess anterior segment and optic disc • Goldmann tonometry • Gonioscopy • Refraction • Risk factors The junior doctor and consultant ophthalmologist examined the 100 patients randomised into the study in	**Inter-observer** (consultant-optometrist) **agreement for *all management decisions* (1-5)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.53** (0.39 - 0.67) **(moderate)** 95% CI calculated by NCC-AC using SE 0.07 from study	**Funding:** Scottish Executive Health Department **Limitations:** The method of weighting of the kappa statistic was not clearly defined and the kappa value agreement scale was not mentioned. It was assumed to be from (Landis and Koch 1977) **Additional Outcomes:** **Notes:** The community optometrists were masked to randomised patient selection. Participants were required not to disclose details of previous consultations.
			Inter-observer (junior doctor–consultant) **agreement for *all management decisions* (1-5)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.45** (0.31 - 0.59) **(moderate)** 95% CI calculated by NCC-AC using SE 0.07 from study	
			Inter-observer (junior doctor–optometrist) **agreement for *all management decisions* (1-5)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.45** (0.31 - 0.59) **(moderate)** 95% CI calculated by NCC-AC using SE 0.07 from study	
			Inter-observer (consultant-optometrist) **agreement for *diagnosis* of glaucoma (4-5 v 1-3)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.70** (0.54 - 0.87) **(substantial)** 95% CI calculated by NCC-AC using SE 0.083 from study	
			Inter-observer (junior doctor–consultant) **agreement for *diagnosis* of glaucoma (4-5 v 1-3)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.54** (0.35 - 0.73) **(moderate)** 95% CI calculated by NCC-AC using SE 0.098 from study	
			Inter-observer (junior doctor–optometrist) **agreement for *diagnosis* of glaucoma (4-5 v 1-3)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.22** (0.02 - 0.42) **(fair)** 95% CI calculated by NCC-AC using SE 0.101 from study	
			Inter-observer (consultant-optometrist) **agreement for *treatment required* (3-5 v 1-2)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.72** (0.57 - 0.86) **(substantial)** 95% CI calculated by NCC-AC using SE 0.076 from study	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		the hospital out patient department with same tests except for IOP measurements	**Inter-observer** (junior doctor–consultant) **agreement for *treatment required* (3-5 v 1-2)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.55** (0.37 - 0.73) **(moderate)** 95% CI calculated by NCC-AC using SE 0.09 from study	
			Inter-observer (junior doctor–optometrist) **agreement for *treatment required* (3-5 v 1-2)**** weighted kappa statistic κ_w	Mean (95%CI) κ_w = **0.62** (0.45 - 0.79) **(substantial)** 95% CI calculated by NCC-AC using SE 0.088 from study	
			Diagnosis of glaucoma (with reference standard defined by consultant)	**Group 1** Sensitivity: **0.76** (95% CI: 0.57-0.89) Specificity: **0.93** (95% CI: 0.85-0.97) **Group 2** Sensitivity: **0.66** (95% CI: 0.48-0.81) Specificity: **0.89** (95% CI: 0.80-0.95)	
			Treatment of glaucoma (with reference standard defined by consultant)	**Group 1** Sensitivity: **0.73** (95% CI: 0.57-0.85) Specificity: **0.96** (95% CI: 0.88-0.99) **Group 2** Sensitivity: **0.64** (95% CI: 0.47-0.78) Specificity: **0.90** (95% CI: 0.80-0.95)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Banes et al., 2000[8] **Study design:** Prospective observational Observer masked	**Patient group:** patients from general glaucoma clinic. Moorfields Eye Hospital Some patients had other ocular pathologies. Most patients had a diagnosis of POAG and were on medical treatment **Inclusion criteria:** NR **<u>All patients</u>** **N:** 54 **Age (mean):** NR **M/F:** NR No demographic data was reported	**Group 1:** 1 senior optometrist **Group 2:** 1 general ophthalmologist (research fellow) **Examination methods:** Visual fields were carried out by a technician before assessment. Both optometrist and research fellow carried out the following: • Clinical history of medication including adverse events • Slit lamp biomicroscopy to assess anterior segment and optic disc o VCD o Drawing of disc o Haemorrhages o Disc size • VF (24-2) plots were considered o Stable o Progressive o Non-glaucoma o Unreliable • Goldmann tonometry • Gonioscopy • Management of patient according to clinical state was assessed o Continue with treatment o Change treatment o Stop treatment o Consider surgery • Length of time to next	**Inter-observer agreement for visual field assessment (right eyes)** kappa statistic κ* (% agreement)	= **0.81 (very good)** (92%) (3 eyes had missing data and 4 eyes were disagreed upon)	**Funding:** NR **Limitations:** • No confidence intervals for kappa • The kappa value agreement scale was not mentioned. It was assumed to be from (Landis and Koch 1977) **Additional Outcomes:** **Notes:** * kappa was calculated excluding missing values Patients were randomly distributed to optometrist and research fellow by clerk but the optometrist did not see any postoperative or complicated cases.
			Inter-observer agreement for visual field assessment (left eyes) kappa statistic κ* (% agreement)	= **0.80 (good)** (91%)	
			Inter-observer agreement for management recommendations (right eyes) kappa statistic κ* (% agreement)	= **1.00 (very good)** (100%) (Group 2 had not recorded data for 3 eyes)	
			Inter-observer agreement for management recommendations (left eyes) kappa statistic κ* (% agreement)	= **0.93 (very good)** (98%) (6 eyes had missing data and 1 eye was disagreed upon)	
			Inter-observer agreement for follow up recommendations kappa statistic κ* (% agreement)	= **0.97 (very good)** (98%) (5 eyes had missing data and 1 eye was disagreed upon)	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		appointment o < 2 months o 3 months o 6 months o 1 year o Discharge			The research fellow was masked to the observations of the optometrist

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat e**tc**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Banes et al., 2006[7] **Study design:** Prospective + Retrospective observational study	**Patient group:** 350 patients attending glaucoma outpatient services at Moorfields, UK **Inclusion criteria:** • Diagnosis of glaucoma (POAG, CACG, secondary and NTG) or OHT **Exclusion criteria:** • New and postoperative patients **<u>All patients</u>** **N:** 350 **Age (median):** NR **M/F:** NR Dropouts: 1 (one hospital record could not be retrieved) No demographic data was reported	**Group 1** 4 certified optometrists with a College of Optometry diploma in glaucoma in hospital setting with patient assessment and management experienced gained from 3 – 10 years of 1-2 half day sessions/week. Training consisted of patient assessments in supportive environment with access to an ophthalmologist. **Group 2** 3 medical clinicians (associate specialists) working part-time in glaucoma clinics for ≥ 10 years **Group 3** 2 consultant ophthalmologists **retrospectively** reviewed the patient records and clinical decisions and made independent management decisions **Examination methods:** Optic disc assessment for glaucomatous damage or normal disc was performed independently of the main study using 134 stereo pairs of disc photographs. Results were compared to previously published data. All patients had a visual field test performed by a technician before clinical assessment. The optometrists	**Detection of glaucomatous disc** using 134 stereo pairs (with glaucomatous damage defined checking against previously published data)	**Group 1** Sensitivity: range 77.8% - 88.2% Specificity: range 76.0% - 79.0% **Group 2** Sensitivity: range 64.7% - 74.2% Specificity: range 82.3% - 93.0%	**Funding:** NR **Limitations:** Mean kappa statistic not reported with confidence intervals **Additional outcomes:** **Notes:** Patients allocated by clinic clerk on a sequential basis to specialist ophthalmologist or optometrist (50 patients each) ***Weighted kappa statistic κ_w** Weights assigned for time to next clinical appointment: 1.0 = agreement; 0.75 = 1 step away disagreement; 0.5 = 2 steps away disagreement ; 0.25 = 3 steps away disagreement, 0 = 4 steps away disagreement and disagreement for discharge and missing data
			Inter-observer agreement for visual field status (kappa statistic & % agreement)	**Group 3 (Consultant 1) v Group 1** κ = 0.33 **fair** (55%) **Group 3 (Consultant 2) v Group 1** κ = 0.27 **fair** (54%) Mean κ = **0.30 fair** **Group 3 (Consultant 1) v Group 2** κ = 0.22 **fair** (44%) **Group 3 (Consultant 2) v Group 2** κ = 0.21 **fair** (43%) Mean κ = **0.22 fair**	
			Inter-observer agreement for clinical management 1 (kappa statistic & % agreement)	**Consultant 1 v Group 1** (certified optometrists) κ = 0.67 **good** (79%) N=199 (3% missing data) **Consultant 1 v Group 2** (general ophthalmologists) κ = 0.52 **moderate** (71%) N=150 (5.3% missing data)	
			% agreement for clinical management 2	Consider cataract surgery: **Group 3 (Consultant 1) v Group 1** 94% **Group 3 (Consultant 1) v Group 2** 91% Consider glaucoma surgery: **Group 3 (Consultant 1) v Group 1** 95% **Group 3 (Consultant 1) v Group 2** 99% Reinforce Compliance: **Group 3 (Consultant 1) v Group 1** 97% **Group 3 (Consultant 1) v Group 2** 99% Discuss with consultant:	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		and medical clinicians then performed a structured clinical assessment on each of their 50 patients then used the clinical data to make management decisions on 5 aspects of patient care: 1. Visual field status (stable, progression, unreliable, non-glaucoma, other) 2. Clinical management 1 (no treatment, continue, start/increase treatment, reduce) 3. Clinical management 2 (consider glaucoma surgery, consider cataract surgery, change treatment due to intolerance, reinforce compliance, discuss with consultant) 4. Planned tests (disc photographs, HRT, VF, IOP phasing 5. Time to next appointment in months (1-2, 3, 6 9 12, discharge)		**Group 3 (Consultant 1) v Group 1** 72% **Group 3 (Consultant 1) v Group 2** 81%	Kappa value agreement 0.00 to 0.2 = poor 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = good 0.81 to 1.00 = very good
			% agreement for planning of tests	Visual Field: **Group 3 v Group 1** mean 62% (C1 & C2) **Group 3 v Group 2** mean 54% (C1 & C2) Imaging: **Group 3 v Group 1** mean 73% (C1 & C2) **Group 3 v Group 2** mean 61% (C1 & C2) Phasing: **Group 3 v Group 1** mean 98% (C1 & C2) **Group 3 v Group 2** mean 100% (C1 & C2) Disc Photo: **Group 3 v Group 1** mean 91% (C1 & C2) **Group 3 v Group 2** mean 100% (C1 & C2)	
			Next clinic appointment weighted kappa statistic κ_w * and % agreement	**Group 3 (Consultant 1) v Group 1** (certified optometrist) κ_w = 0.35 **fair** (79%) **Group 3 (Consultant 1) v Group 2** (general ophthalmologist) κ_w = 0.29 **fair** (73%)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Harper et al., 2000[56] **Study design:** Retrospective observational study	**Patient group:** 48 optic disc stereophotographs retrospectively selected from of glaucomatous and non glaucomatous patients attending glaucoma service in Greenwich Hospital, UK **Inclusion criteria:** Photographs that were representative of a wide range of disc appearances classified using a visual analogue scale (VAS) 0= definitely non-glaucomatous and 100= definitely glaucomatous by a glaucoma specialist. Matched visual field data was not available for the stereophotographs **<u>All patients</u>** **N:** 48 **Age (median):** NR **M/F:** NR **Glaucomatous damage (defined by VAS**): • **Definitely non-glaucomatous ≤10):** 11 • **Definitely glaucomatous ≥90):** 15 • **Suspicious (11-89):** 22 Patient demographics were not reported	**Group 1** 3 optometrists with 4 years accredited training ≥ 4 years post registration experience. None had specialist shared care expertise **Group 2** 2 general ophthalmologists. One SPR and one associate specialist in medical ophthalmology. Neither had sub-speciality training although the associate specialist had responsibility for reporting on fundus/disc photographs **Examination methods:** Photographs had been taken with a standard fundus camera with stereopsis achieved through decentration of camera angle. They were examined through a Carl-Zeiss 2x stereoscopic viewer and standard light box Each observer 1. Estimated vertical cup disc ratio (VCD) 2. Grading of narrowest rim width estimate 3. Haemorrhage present or absent Also graded using simple ranking/ordinal scales	**Inter-observer (ophthal-optom) agreement in estimating VCD** **weighted kappa statistic κ_w *** **Inter-observer (ophthal-optom) agreement in estimating VCD** **1 x standard deviation of difference scores** **Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio** **weighted kappa statistic κ_w *** **Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio** **1 x standard deviation of difference scores** **Inter-observer (ophthal-optom) detection of disc haemorrhage as present or absent** **(kappa statistic - unweighted)** **Inter-observer (ophthal-optom) agreement on neuroretinal rim pallor** **weighted kappa statistic κ_w**	Mean κ_w = **0.46 (moderate)** Range from 0.23 (fair) to 0.64 (substantial) Mean SD = 0.19 (range 0.13 – 0.22) (4/6 mean differences were significantly different $p<0.01$) Mean κ_w = NR Range from 0.29 (fair) to 0.65 (substantial) Mean SD = NR (range 0.09 – 0.15) (3/6 mean differences were significantly different $p<0.01$) Mean κ **= 0.77 (substantial)** Range from 0.61 (substantial) to 0.91 (almost perfect) % agreement ranges from 90-98%) Mean κ_w = **0.23 (fair)**	**Funding:** College of optometrists **Limitations:** • No confidence intervals available for Mean weighted kappa statistic or SD • No patient demographics **Notes:** Observers were presented photographs in a masked and random fashion with at least 5 days between the 2 assessments of each photograph ***Weighted kappa statistic κ_w** Weights assigned to each observation for VCD were equal to 1 minus (difference between estimates). 0.0 difference = 1, 0.1 difference = 0.9 weight etc until 1.0 difference = 0. Smaller disagreements were weighted more heavily Kappa value agreement (Landis and Koch 1977)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		4. Focal pallor of neuroretinal rim 5. Extent of peri-papillary atrophy 6. Steepness of cup-edge 7. Cribriform sign as present or absent	*		-1.00 to 0 = poor 0.01 to 0.2 = slight 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = substantial 0.81 to 0.99 = almost perfect +1.00 = perfect
			Inter-observer (ophthal-optom) agreement on peri-papillary atrophy **weighted kappa statistic κ_w ***	Mean κ_w = **0.45 (moderate)**	
			Inter-observer (ophthal-optom) agreement on steepness of cup edge **weighted kappa statistic κ_w ***	Mean κ_w = **0.50 (moderate)**	
			Inter-observer (ophthal-optom) agreement on cribriform sign **weighted kappa statistic κ_w ***	Mean κ_w = **0.48 (moderate)**	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Harper et al., 2001[55] **Study design:** Retrospective observational study	**Patient group:** 48 optic disc stereophotographs retrospectively selected from of glaucomatous and non glaucomatous patients attending glaucoma service in Greenwich Hospital, UK **Inclusion criteria:** Photographs that were representative of a wide range of disc appearances classified using a visual analogue scale (VAS) 0= definitely non-glaucomatous and 100= definitely glaucomatous by a glaucoma specialist. Matched visual field data was not available for the stereophotographs **<u>All patients</u>** **N:** 48 **Age (median):** NR **M/F:** NR **Glaucomatous damage (defined by VAS**): • **Definitely non-glaucomatous ≤10):** 11 • **Definitely glaucomatous ≥90):** 15 • **Suspicious (11-89):** 22 Patient demographics were not reported	**Group 1** 6 optometrists with 4 years accredited training. 2 had 1 year of post-registration experience, 2 had 4 years of post-registration experience and 2 had ≥ 10 years of post-registration experience. None had been involved in shared care schemes or had specialist training. All employed full or part-time in primary care optic role. **Group 2** 6 general ophthalmologists: 2 SPR and 2 SHOs and 2 consultants with subspecialty expertise in glaucoma. **Examination methods:** Photographs had been taken with a standard fundus camera with stereopsis achieved through decentration of camera angle. They were examined through a Carl-Zeiss 2x stereoscopic viewer and standard light box Each observer 1. Estimated vertical cup disc ratio (VCD) uncorrected for disc size 2. Grading of narrowest rim width estimate 3. Haemorrhage present or absent	**Inter-observer (ophthal-optom) agreement in estimating VCD** **weighted kappa statistic κ_w *** **Inter-observer (ophthal-optom) agreement in estimating VCD** **1 x standard deviation of difference scores** **Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio** **weighted kappa statistic κ_w *** **Inter-observer (ophthal-optom) agreement in estimating rim:diameter ratio** **1 x standard deviation of difference scores** **Inter-observer (ophthal-optom) detection of disc haemorrhage as present or absent** **(unweighted kappa statistic)**	Mean (95%CI) κ_w = **0.36** (0.31 - 0.41) **(fair)** Range for κ_w from 0.06 (slight) to 0.63 (substantial) Mean (95%CI) SD = 0.18 (0.17 - 0.20) Range 0.10 – 0.28 (25/36 mean differences were significantly different $p<0.01$ or <0.001 or <0.0001) Mean (95%CI) κ_w = **0.35** (0.29 - 0.41) **(fair)** Range for κ_w from -0.01 (poor) to 0.77 (substantial) Mean (95%CI) SD = 0.11 (0.11 - 0.12) Range 0.08 – 0.15 (23/36 mean differences were significantly different $p<0.01$ or <0.001 or <0.0001) Mean (95%CI) κ **= 0.42** (0.37 – 0.47) **(moderate)** Range 0.12 (slight) to 0.72 (substantial)	**Funding:** NR **Limitations:** • No patient demographics **Notes:** Observers were presented photographs in a masked and random fashion with at least 5 days between the 2 assessments of each photograph ***Weighted kappa statistic** Weights assigned to each observation for VCD were equal to 1 minus (difference between estimates). 0.0 difference = 1, 0.1 difference = 0.9 weight etc until 1.0 difference = 0. Smaller disagreements were weighted

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		The features were discussed between each observer and the researcher prior to grading. All 12 observers had opportunity to read instructions for grading criteria			more heavily Kappa value agreement (Landis and Koch 1977) -1.00 to 0 = poor 0.01 to 0.2 = slight 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = substantial 0.81 to 0.99 = almost perfect +1.00 = perfect

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Service Provision (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Spry, 1999[142] & Gray, 2000[52] [Bristol Shared Care Glaucoma Study] **Study design:** RCT **Evidence level:** + **Duration of follow-up:** 2 years Computer generated random numbers and allocation concealment	**Patient group:** glaucoma patients and glaucoma suspects attending glaucoma clinic **Setting:** Bristol Eye Hospital, UK **Inclusion criteria:** • 50 years • Glaucoma suspects • Stable (no change in visual field (VF) over last year) glaucoma • Primary open angle glaucoma • Pigment dispersion glaucoma • Pseudoexfoliative glaucoma • Informed consent • Ability to cooperate with examination • Snellen visual acuity (VA) ≥ 6/18 in both eyes **Exclusion criteria:** • <50 years • Unstable glaucoma • Normal tension glaucoma • Secondary glaucoma • Narrow angle glaucoma • Other coexisting ocular pathology • Extensive field loss (>66/12 missed points on Henson 132 point threshold related suprathreshold examination	**Group 1** Routine follow up** in Hospital Eye Service (HES) comprising by a general ophthalmologist: • VF analysis with Henson CFS2000/CFA3000 • Single IOP measurement using Goldmann Applanation Tonometry (GAT) • Vertical cup-disc ratio (VCD) using direct ophthalmoscopy or indirect binocular ophthalmoscopy **Group 2** Structured 6 monthly follow-up at specially trained (instruction through lectures and demonstrations from study researchers) Community Optometrist (CO) comprising: • VF analysis using Henson CFA 3000 132 point threshold related suprathreshold examination • Repeat VF examination on 50% patients • Single IOP measurement using GAT	**Mean number of points missed on visual field testing ± SD** ***Better Eye***	**Group 1:** 7.9 ± 12.0 **Group 2:** 6.8 ± 10.8 **Difference between means:** 0.07 (95% CI: -1.86, 2.04) **p value:** 0.94 **(ANCOVA)*** **not signif.**	**Funding:** MRC, International Glaucoma Association, R&D Directorate NHS Executive South and West and Avon Health Authority **Limitations:** **Notes:** ***ANCOVA**: analysis of covariance was performed for each outcome variable comparing the 2 follow up groups ***adjusting for baseline measurements.*** Control was also considered for age, sex, time from recruitment to follow up, treatment at baseline, treatment at any time (any/none) and diagnosis (glaucoma suspect/established POAG) **$Adjusted Intraclass Correlation Coefficient (ICC):** The ICC is an equivalent to a quadratic weighted kappa statistic as a
			Mean number of points missed on visual field testing ± SD ***Worse Eye***	**Group 1:** 20.2 ± 21.6 **Group 2:** 18.3 ± 19.9 **Difference between means:** 0.04 (95% CI: -3.49, 3.40) **p value:** 0.98 **(ANCOVA)*** **not signif.**	
			Mean IOP (mmHg) ± SD ***Better Eye***	**Group 1:** 19.3 ± 5.1 **Group 2:** 19.3 ± 4.7 **Difference between means:** 0.26 ± (95% CI: -1.21, 0.68) **p value:** 0.59 **(ANCOVA)*** **not signif.**	
			Mean IOP (mmHg) ± SD ***Worse Eye***	**Group 1:** 19.1 ± 5.5 **Group 2:** 19.0 ± 5.3 **Difference between means:** 0.53 ± (95% CI: -1.58, 0.51) **p value:** 0.32 **(ANCOVA)*** **not signif.**	
			Cup disc ratio ± SD ***Better Eye***	**Group 1:** 0.72 ± 0.12 **Group 2:** 0.72 ± 0.13 **Difference between means:** 0.00 (95% CI: -0.02, 0.03) **p value:** 0.70 **(ANCOVA)*** **not signif.**	
			Cup disc ratio ± SD ***Worse Eye***	**Group 1:** 0.74 ± 0.13 **Group 2:** 0.74 ± 0.14 **Difference between means:** 0.00 (95% CI: -0.03, 0.03) **p value:** 0.70 **(ANCOVA)*** **not signif.**	
			VCD (inter centre agreement) ***Right Eye***	**Mean Difference:** -0.05 (95% CI: -0.03, -0.07) **$Adjusted ICC: 0.50** (moderate agreement) N=360	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
	• Best corrected VA in either eye worse than 6/18 **<u>All patients</u>** **N:** 403 **<u>Group 1 (HES)</u>** **N:** 200 **Age (mean ± SD):** 69.4 ± 8.8 **M/F:** 115/85 **Mean glaucoma suspects** **Male:** 48 **Female:** 30 **Family history:** 35 **Previous cataract extraction:** 14 **LogMAR both eyes (mean ± SD):** 0.06 ± 0.18 **Drop outs:** 38 (died = 7, moved = 2, general health = 6, lost to follow up = 23) **<u>Group 2 (CO)</u>** **N:** 203 **Age (mean ± SD):** 68.0 ± 8.3 **M/F:** 103/100 **Mean glaucoma suspects** **Male:** 51 **Female:** 44 **Family history:** 48 **Previous cataract extraction:** 8 **LogMAR both eyes (mean ± SD):** 0.06 ± 0.17 **Drop outs:** 19 (died = 5, moved = 4, general health = 3, other = 7)	• VCD using direct ophthalmoscopy or indirect binocular ophthalmoscopy (dilated pupil) **Examination methods:** A research clinic reference standard (RCRS) examination was performed on each patient at baseline pre-randomisation and 2 year follow up comprising: • VF analysis using Henson CFA 3000 132 point threshold related suprathreshold examination • Repeat VF examination • Triple IOP measurement using GAT • VCD using direct ophthalmoscopy or indirect binocular ophthalmoscopy (dilated pupil) • Stereophotographic analysis of VCD by observer 1 • Stereophotographic analysis of VCD by observer 2	**VCD (inter centre agreement)** ***Left Eye***	**Mean Difference:** 0.05 (95% CI: 0.03, 0.07) **$Adjusted ICC: 0.54** (moderate) N=358	chance corrected measure of agreement which corrects for systematic bias, weighting discrepancies according to square of the differences between the paired measurements. **ICC = <0.2** "slight agreement"; **ICC = 0.21-0.40** "fair agreement"; **ICC = 0.41-0.60** "moderate agreement; **ICC = 0.61-0.80** "substantial agreement; **ICC = ≥ 0.80** "almost perfect agreement. **For HES group mean time to first follow up 10.7 ± 5.4 months (range 3 – 24 months) Median number of visits within 2 year period was 2.8 (range 0-8) **Additional outcomes:** RCRS v HES (all outcomes and RCRS v CO (all outcomes
			IOP mmHg (inter centre agreement) ***Right Eye***	**Mean Difference:** 0.4 (95% CI: -0.05, 0.85) **$Adjusted ICC: 0.45** (moderate) N=388	
			IOP mmHg (inter centre agreement) ***Left Eye***	**Mean Difference:** 0.6 (95% CI: 0.13, 1.07) **$Adjusted ICC: 0.40** (fair) N=388	
			VF points missed (inter centre agreement) ***Right Eye***	**Mean Difference:** 1.1 (95% CI: -0.38, 2.58) **$Adjusted ICC: 0.55** (moderate) N=287	
			VF points missed (inter centre agreement) ***Left Eye***	**Mean Difference:** 0.7 (95% CI: -0.80, 2.20) **$Adjusted ICC: 0.61** (substantial) N=287	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Service Provision (continued)

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
Theodossiades & Murdoch, 2001[148] **Study design:** Prospective observational	**Patient group:** Volunteers from Moorfields Eye Hospital glaucoma clinics, UK **Inclusion criteria:** Wide range of normal and glaucomatous disc features **<u>All patients</u>** **N:** 50 **Age (median):** NR **M/F:** NR **Glaucomatous damage (defined by consultant):** • **No glaucoma:** 27 • **Early glaucoma:** 4 • **Moderate glaucoma:** 5 • **Advanced glaucoma:** 14 Patient demographics were not reported	**Group 1** 8 community optometrists based in high street optometric practices. 6 also worked part-time in the hospital eye service but not for glaucoma. Optometrists received 2 hours of lectures on assessment of optic nerve head **Group 2** Consultant ophthalmologist with specialist interest in glaucoma **Examination methods:** Both undilated eyes of each patient were first examined by the consultant ophthalmologist using slit lamp biomicroscopy and one eye selected for examination by optometrist. Optometrists assessed one undilated eye through a direct ophthalmoscope of each patient for the following parameters: 1. Vertical disc diameter 2. Vertical cup disc ratio (VCD) 3. Neuroretinal configuration 4. Cup shape 5. Neuroretinal rim colour 6. Vessel configuration 7. Haemorrhage 8. Extent of peri-papillary atrophy 9. Health status of optic nerve head These were then used to give a final opinion on presence or absence of	**Inter-observer agreement in Vertical disc diameter** weighted kappa statistic κ_w *	Mean (95%CI) κ_w = **0.34** (0.26 - 0.42) **(fair)**	**Funding:** International Glaucoma Association **Limitations:** • No patient demographics • Weighting method for VCD and vertical disc diameter was not reported • Observer masking was not reported • Patients were not recruited in a randomised or consecutive fashion. **Notes:** Kappa value agreement based on (Landis and Koch 1977) 0.00 to 0.2 = poor 0.21 to 0.40 = fair 0.41 to 0.60 = moderate 0.61 to 0.80 = good 0.81 to 1.00 = very
			Inter-observer agreement in VCD weighted kappa statistic κ_w *	Mean (95%CI) κ_w = **0.84** (0.81 - 0.87) **(very good)**	
			Inter-observer agreement in Neuroretinal configuration kappa statistic κ_w	Mean (95%CI) κ_w = **0.67** (0.58 - 0.76) **(good)**	
			Inter-observer agreement in Cup shape kappa statistic κ_w	Mean (95%CI) κ_w = **0.66** (0.58 - 0.74) **(good)**	
			Inter-observer agreement in Neuroretinal rim colour kappa statistic κ_w	Mean (95%CI) κ_w = **0.32** (0.25 - 0.38) **(fair)**	
			Inter-observer agreement in Vessel configuration kappa statistic κ_w	Mean (95%CI) κ_w = **0.53** (0.40 - 0.65) **(moderate)**	
			Inter-observer agreement in Haemorrhage kappa statistic κ_w	Mean (95%CI) κ_w = **0.67** (0.45 - 0.89) **(good)**	
			Inter-observer agreement in Peri-papillary atrophy kappa statistic κ_w	Mean (95%CI) κ_w = **0.22** (0.14 - 0.29) **(fair)**	

Study details	Patients	Observer Groups	Outcome Measures	Effect Size	Comments
		glaucomatous damage	**Inter-observer agreement in Health status of optic nerve head** kappa statistic κ_w	Mean (95%CI) κ_w = **0.62** (0.53 - 0.70) **(good)**	good
			Health status of optic nerve head (reference standard defined consultant)	Sensitivity: **0.90** (95% CI: 0.86 - 0.94) Specificity: **0.73** (95% CI: 0.66 - 0.80)	

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat **etc**

Evidence Table 23 Patient Views

Study details	Patients	Intervention	Outcome measures	Effect size	Comments
Day et al., 2006[32] **Study design:** Prospective observational cohort **Evidence level:** **Duration of follow-up:** N/A	**Patient group:** Consecutively recruited patients from outpatient clinics. **Setting:** USA **Inclusion criteria:** • > 18 years • POAG or OHT • On medication in at least 1 eye for 30 days prior to study • Adequate visual acuity • Mental ability to read and understand English **Exclusion criteria:** • Patients with clinically significant medical or psychiatric condition • Those who had participated in another trial within 30 days prior to study • Unable to give informed consent • Unable to understand trial procedures • Those with previous laser or surgery with previous 2 months **<u>All patients</u>** **N:** 250	The **Treatment Satisfaction Survey-Intraocular Pressure (TSS-IOP)** - owned by Pfizer, Inc. - is a survey focussing on patient satisfaction and perception of their glaucoma medication and patient compliance. The survey consists of 15 validated questions falling under categories below: • Effectiveness (satisfaction scale) o Preventing future vision problems o Reducing current vision problems • Side effects – eye irritation (bother scale) o Prolonged burning or stinging o Grittiness or sandiness o Stickiness or crustiness o Dry eyes • Eye appearance – hyperaemia (bother scale) o Peoples' reaction to red eye o Self-consciousness of red eye o Overall cosmetic appearance • Ease of administration (satisfaction scale) o Number of times drops applied o Time of day for application o Ease of remembering to	**Treatment satisfaction and dosing frequency Mean TSS-IOP score ± SD**	**TSS-IOP Effectiveness** Single medications (n=151) 79.1 ± 15.4 Multiple medications (n=99) 73.7 ± 18.0 **P =0.01** **TSS-IOP Side Effects** Single medications (n=151) 93.4 ± 12.7 Multiple medications (n=99) 88.7 ± 15.2 **P =0.01** **TSS-IOP Irritation** Single medications (n=151) 93.4 ± 11.1 Multiple medications (n=99) 87.5 ± 17.8 **P =0.001** **TSS-IOP Convenience of use** Single medications (n=151) 82.54 ± 14.2 Multiple medications (n=99) 77.1 ± 16.8 **P =0.007** **TSS-IOP Ease of use NR**	**Funding:** Pfizer, Inc. CA, USA. **Limitations:** • Statistical analysis was not explained. • TSS-IOP scoring system was not clearly explained • Study reports correlation analysis between TSS-IOP items and items from an invalidated additional questionnaire **Additional outcomes:** Correlation between TSS-IOP items and physician reported ratings of IOP control, side effects, compliance and problems with
			Differences between specific single glaucoma medications (n=148) Mean TSS-IOP score ± SD	**TSS-IOP Convenience of use** Beta-blockers (n=34) 85.8 ± 14.5 PGA (n=80) 83.6 ± 14.0 CAI (n=22) 79.3 ± 14.3 Sympathomimetic (n=12) 73.6 ± 11.1 P values NR. NCC-AC calculate using *t* test with equal variance BB v PGA **p=Not signif.** BB v CAI **p=Not signif.** BB v sympathomimetics **p=0.01** PGA v CAI **p=Not signif.** PGA v sympathomimetics **p=0.02** CAI v sympathomimetics **p=Not signif.**	
			Differences between specific glaucoma medications Mean TSS-IOP score ± SD	**TSS-IOP Eye appearance** Beta-blockers (n=34) 99.3 ± 3.2 PGA (n=80) 90.7 ± 17.8 CAI (n=22) 93.6 ± 8.1 sympathomimetics (n=12) 88.2 ± 27.2 P values NR. NCC-AC calculate using *t* test	

Study details	Patients	Intervention	Outcome measures	Effect size	Comments
	Age (mean ± SD): 64.6 ± 13.1 **M/F:** 109/141 **History of elevated IOP (years):** 8.4 ± 7.8 **Race** White: 138 African-American: 109 Hispanic: 3 **Iris Colour** Brown: 142 Blue: 67 Other: 41 **Employment** Retired: 134 Full or part time: 99 Unemployed: 17 **Number of medications** **Monotherapy (n=148):** β-blockers: 34 PGA: 80 CAI: 22 Sympathomimetics: 12 **Adjunctive therapy (n=102):** β-blockers: 48 PGA: 85 CAI: 49 Sympathomimetics: 31	use • Convenience of use (satisfaction scale) o Ease of delivery of correct amount rather than missing or too much o Ease of angling head when sitting or standing to apply o Ease of consistently applying correct amount Items were scored on either a 5 or 7 point scale from 'Extremely satisfied' or 'Extremely Bothered' to 'Extremely dissatisfied' or "Not bothered' Patients had a full medical and ocular history taken and completed a supplemental non-validated questionnaire about their expectations of topical medication. Patients then completed the TSS-IOP validated questionnaire. Patients had a clinical examination as part of routine care and then completed a questionnaire regarding assessment of the patients' treatment, tolerance of medicine and compliance. 25 patients were asked to return for ±a second visit to complete the questionnaire again to evaluate test-retest reliability		with unequal variance BB v PGA **p=0.0001** BB v CAI **p=0.004** BB v sympathomimetics **p=0.19 Not ignif.** PGA v CAI **p=Not signif.** PGA v sympathomimetics **p=Not signif.** CAI v sympathomimetics **p=Not signif.**	self-administration **Notes:**

Abbreviations: NR=not reported, NA=not applicable, M/F=male/female, N=total number of patients randomised, SD=Standard Deviation, SE(M)=Standard Error (of the mean), ITT – Intention to Treat etc

Evidence Table 24 Economic Evidence

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Kymes et al., 2006[80] USA **Economic analysis:** Cost Utility analysis **Study design** Decision analysis* **Time horizon:** Life-time **Discount rates:** Costs: 3% Effects: 3%	**Patient group:** patients between 40 and 80 with OHT (IOP between 24mm Hg and 32mm Hg in one eye and between 21mm Hg and 32mm Hg in the other eye, and normal VF and optic disk in both eyes) **<u>All patients</u>** * **N:** 1636 **N with glaucoma:** 0 **M/F:** 705/931 **Mean IOP at baseline (SD):** 24.9 (2.7) **Ethnic origin:** Asian 14, African American 408, Hispanic 59, White 1137, Other 18 **Drop outs:** 228	**Intervention 1:** Treat no one **Intervention 2:** Treat if IOP≥24 mm Hg and annual risk of developing POAG ≥5% **Intervention 3:** Treat if IOP≥24 mm Hg and annual risk of developing POAG≥2% **Intervention 4:** Treat everyone with IOP≥24 mm Hg	Mean QALYs gained per patient (determined by progression and development of cataract)	**intervention 1:** 13.537 **intervention 2:** 13.559 **Intervention 3:** 13.588 **Intervention 4:** 13.587 **p value:** NR	**Funding:** National Eye Institute; National Institutes of Health; Merck Research Laboratories; Pfizer, Inc; Research to prevent Blindness, Inc. **Limitations:** Treatment was a mixture **Notes:** * Based on the Ocular Hypertension Treatment Study
			Mean total life-time cost per patient 2006 US$, cost of medication, cataract surgery, cost associated with POAG progression, cost of blindness. Societal perspective	**Intervention 1: $**4,006 (£ 2,476) **Intervention 2: $**4,086 (£ 2,525) **Intervention 3:** $5,305 (£ 3,278) **Intervention 4:** $11,245 (£ 6,949) **p value:** NR	
			Cost-effectiveness Cost per QALY gained	Int 2 vs Int 1: $3,670 (£2,268) Int 3 vs Int 2: $42,430 (£ 26,222) Int 4 vs Int 3: Int 4 is dominated	
			Sensitivity analysis One-way SA	Sensitive factors were: incidence of POAG without treatment (if less than 1.5%, Int 2 more cost-effective), proportion of people with OHT to be treated, reduction in risk because of medical treatment (if <30% Int 2 more cost-effective), annual probability of progression of a POAG stage, cost of one medication, increased annual risk of cataract surgery, utility loss in stage 1 POAG.	
			Probabilistic sensitivity analysis (Monte Carlo simulation)	At the £20,000/QALY threshold, both Int 1 and Int 3 have a 30% probability of being the most cost-effective, while Int 2 has a 40% probability.	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Stewart et al., 2008[144] USA **Economic analysis:** Cost Utility **Study design** Decision model based on the Ocular Hypertension Treatment Study and Early Manifest Glaucoma Trial. **Time horizon:** 5 years **Discount rates:** Costs: 3% Effects: 0%	**Patient group:** patients with ocular hypertension from the Ocular Hypertension Treatment Study.	**Intervention 1:** No treatment **Intervention 2:** 1 medication for the first 2 years. In the last 3 years: - 1.4 medications in non-progressing patients - 2 medications in 75% of patients that progressed - 3 medications in 15% of patients that progressed Medications could be Prostaglandin Analogues, Beta-Blockers or Brimonidine.	QALYs	**Intervention 1:** 4.45 **Intervention 2:** 4.48 **p value:** NR	**Funding:** NR (one of the authors was employed by Pfizer). **Limitations:** - other relevant outcomes were omitted (e.g. blindness) - limited applicability (US cost data)
			Mean cost per patient 2007 US $, Cost of visits, medications, and tests (central corneal thickness, gonioscopy, IOP, optic disc imaging, refraction, automated visual field).	**Intervention 1:** $ 2,467 (£ 1,525) **Intervention 2:** $ 5,001 (£ 3,091) **p value:** NR	
			Cost-effectiveness incremental cost per QALY gained	Intervention 2 vs Intervention 1 $84,467 (£ 52,200)	
			Sensitivity analysis One-way SA (risk of progression is changed according to risk factors) DSA (costs are changed by + or -10%)	Intervention 2 is cost-effective in one of the following situations: - vertical cup to disc ratio plus 0.7 or more - corneal thickness plus 80µm No change in results	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Bernard 2003[10] France **Economic analysis:** cost-effectiveness **Study design** Decision analysis* **Time horizon:** 2 years and 3 years **Discount rates:** Costs: 3% Effects: 0%	**Patient group:** patients newly diagnosed with open angle glaucoma or ocular hypertension (IOP>21 mmHg and no optic nerve damage).	**Intervention 1:** First-line treatment with a beta-blocker followed by usual care for patients who switch therapy. **Intervention 2:** First-line treatment with latanoprost 0.005% followed by usual care for patients who switch therapy.	Proportion of patients remaining on first-line treatment (after 1 year; after 2 years)	**Int 1:** 46%; 29% **Int 2:** 82%; 73% **p value:** NR	**Funding:** Pharmacia Corporation, Peapack, USA **Limitations:** Clinical outcomes were not compared to other studies. Limited time horizon. **Additional outcomes:** Proportion of patients undergoing surgery (7% for Int 1and 3% for Int 2 over 3 years) **Notes:** * Model inputs were taken from chart reviews. ** Calculated by NCC-AC from incremental cost per IOP-controlled day gained.
			Mean time spent on the initial therapy (months)	**Int 1:** 13.4 **Int 2:** 20.5 **p value:** <0.0001	
			Mean number of therapies used over 2 years (CI)	**Int 1:** 2.08 (± 0.94) **Int 2:** 1.38 (± 0.74) **p value:** <0.0001	
			Mean IOP-controlled days (days) (over 2 years; over 3 years)	**Int 1:** 653; 973 **Int 2:** 703; 1047 **p value:** <0.0001	
			Mean cost per patient (over 2 years; over 3 years) (2002 Euro Cost of management, treatment, surgery)	**Int 1:** € 539 (£ 366); € 817 (£ 556) **Int 2:** € 580 (£ 394); € 844 (£ 574) **p value:** <0.0001	
			Cost-effectiveness Incremental cost per IOP-controlled year gained per patient** (over 2 years; over 3 years)	**Int 2 vs Int 1:** € 299 (£ 204); € 131 (£ 88)	
			Sensitivity analysis One-way sensitivity analysis	The results were sensitive to time to therapy failure, bottle duration, assessment visit schedule for patients who switched treatments, surgical rates, and cost of surgery.	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Day 2004[31] USA **Economic analysis:** Cost consequences **Study design** Retrospective cohort study **Duration of follow-up:** 6 months **Discount rates:** Costs: NA Effects: NA	**Patient group:** adult patients with COAG or OHT in at least one eye whose records were stored in large glaucoma practices in the USA. **<u>All patients</u>** **N:** 1182 (1 eye randomly chosen evaluated) **N with glaucoma:** 922 **M/F:** 510/672 **Drop outs:** 0 **<u>Group 1</u>** **N:** 487 **N with glaucoma:** 361 **Age (mean±SD):** 64.4±14.3 **M/F:** 219/268 **Ethnic origin:** Caucasian 325, African-American 82, Asian 6, Hispanic 12, Other and Unknown 62 **<u>Group 2</u>** **N:** 490 **N with glaucoma:** 401 **Age (mean±SD):** 67±13.9 **M/F:** 207/283 **Ethnic origin:** Caucasian 303, African-American 109, Asian 1, Hispanic 8, other and unknown 69 **<u>Group 3</u>** **N:** 205 **N with glaucoma:** 160 **Age (mean±SD):** 68.9±12.8 **M/F:** 84/121 **Ethnic origin:** Caucasian 114, African-American 30, Asian 1, Hispanic 5, Other and Unknown 55	**Group 1:** Beta-blockers monotherapy as first or second line (71% with Timolol). **Group 2:** Latanoprost monotherapy as first or second line. **Group 3:** Bimatoprost monotherapy as first or second line.	Risk ratio to discontinue therapy compared to group2	**Group 1:** 1.15 (95% CI: 1.03, 1.27) **Group 2:** 1 **Group 3:** 1.08 (95% CI: 1.01, 1.16) **p value:** 0.02	**Funding:** Pfizer, Inc. **Limitations:** No differentiation between treatments used as a first- or second-choice. The short follow-up does not allow including the costs associated with disease progression (e.g. surgery). Mean IOP at baseline not reported. **Additional outcomes:** Main reasons for changing or adding to current medication before 6 months of therapy were IOP not controlled and adverse events. Patient visits were fewer with latanoprost (p=0.01). The number of ocular adverse events was fewer with beta-blockers.
			IOP at the last visit before the therapy is changed (mmHg±SD)	**Group 1:** 17.9±3.7 **Group 2:** 17.3±3.9 **Group 3:** 18.0±3.6 **p value:** <0.0001	
			Mean cost per patient per 6months of therapy 2004 US$ Direct costs only: cost of drugs (average wholesale price) + visits and procedures resulting from adverse events as well. Cost of drug based on both eyes receiving treatment and assuming perfect compliance	**Group 1:** $ 119 (76+43) (£ 74) **Group 2:** $ 154 (116+38) (£ 95) **Group 3:** $ 164 (124+40) (£ 101) **p value:** <0.0001 (drugs), p=0.07 (visits and procedures)	
			Cost-effectiveness	NR	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Goldberg 2006[48] USA **Economic analysis:** cost-effectiveness **Study design** Decision analysis based on RCT* **Time-horizon:** 1 year **Discount rates:** Costs: NA Effects: NA	**Patient group:** patients with POAG or OHT (IOP 22-34 mmHg) in at least one eye. **<u>All patients</u>*** **N:** 715 **M/F:** 307/408 **Drop outs:** 86 **Ethnic origin:** 583 non-black, 132 black **<u>Group 1</u>** **N:** 241 **Age (mean):** 61 **M/F:** 101/140 **Drop outs:** 27 **Mean IOP at baseline:** NR **Ethnic origin:** 195 non-black, 46 black **<u>Group 2</u>** **N:** 474 **Age (mean):** 61.7 **M/F:** 206/268 **Drop outs:** 59 **Mean IOP at baseline:** NR **Ethnic origin:** 388 non-black, 86 black	**Group 1:** Timolol twice daily morning and evening as first-line. **Group 2:** One drop of Bimatoprost 0.03% once-daily in the evening as first-line.	Percentage of patients achieving target pressure (17mmHg) after 12 months.	**Group 1:** 37%, 27%, 16%, 9%, 5% **Group 2:** 58%, 47%, 31%, 21%, 12% **p value:** <0.05	**Funding:** Allergan, Inc. **Limitations:** The study assumes success is achieved after dual therapy and patients are perfectly compliant. The study does not consider surgical treatment, adverse events or endpoints other than IOP (e.g. blindness). Limited time horizon. **Notes:** *Higginbotham 2002[62]. Data from another RTC excluded because it has a 3-month follow-up. ** calculated by NCC-AC according to costs and algorithm reported in the study.
			Mean annual cost per patient** 2003 US$, (cost of initial and adjunctive medication based on average wholesale prices + cost of visits, if target pressure 17mmHg)	**Group 1: $**828 (£ 517), $ 896 (£ 559), $964 (£ 601), $1032 (£ 644), $1063 (£ 663). **Group 2:** $1043 (£ 651), $1066 (£665), $1112 (£ 694), $1151 (£ 718), $1183 (£ 738). **p value:** NR	
			Cost-effectiveness** Incremental cost per additional treatment success	**Group 2 vs Group 1:** $1024 (£ 639)	
			Sensitivity analysis one-way sensitivity analysis	ICER was $850 (£ 530), $987 (£ 616), $992 (£ 619), $1714 (£ 1069) if target pressure was respectively16mmHg, 15mmHg, 14mmHg, 13mmHg. Results were sensitive to the average wholesale prices (if branded Timolol was used, bimatoprost would become at least 30% more cost effective at target IOP 17), to changes in treatment success rates, to the adjunctive agent chosen (if brimonidine, bimatoprost would be dominant).	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Halpern 2002[54] USA **Economic analysis:** Cost consequences **Study design** Decision analysis based on a RCT (Netland 2001) **Duration of follow-up:** 1 year **Discount rates:** Costs: NA Effects: NA	**Patient group:** black patients with POAG or OHT. **<u>All patients</u>** **N:** 132 **M/F:** 56/76 **Drop outs:** 19 **<u>Group 1</u>** **N:** 40 **Age (mean):** 62.3 **M/F:** 15/25 **Drop outs:** 7 **Mean IOP at baseline:** 25.8 **<u>Group 2</u>** **N:** 43 **Age (mean):** 58.6 **M/F:** 18/25 **Drop outs:** 3 **Mean IOP at baseline:** 26.2 **<u>Group 3</u>** **N:** 49 **Age (mean):** 62.6 **M/F:** 23/26 **Drop outs:** 9 **Mean IOP at baseline:** 25.3	**Group 1**: Timolol 0.5%, one drop at 8 AM and at 8 PM as first-line. **Group 2:** Latanoprost 0.005% One drop at 8PM plus placebo at 8AM as first-line. **Group 3:** Travoprost 0.004% One drop at 8PM plus placebo at 8AM as first-line.	Mean IOP during the 1-year follow-up (mm Hg±SD)	**Group 1:** 20.5±3.4 **Group 2:** 18.7±2.4 **Group 3:** 17.3±2.5 **p value:** <0.05 (group 1 and 2 vs 3)	**Funding:** Alcon Research, Ltd. **Limitations:** It is not clearly stated if the costs of medication have been included. It is not clear when the IOP at follow-up was measured. Limited follow-up. **Notes:** *Calculated by averaging various algorithms that link IOP with visual field defect ** Inpatient costs: increased VFDS x mean number of hospitalisation per year due to severe visual field defect x average length of stay x cost per day as reimbursed by Medicare. Outpatient costs: Medicare 2000 reimbursement values x increased VFDS
			Mean increase in visual field progression rates*	**Group 2 vs Group 3:** 19% **Group 1 vs Group 3:** 27.5% **p value:** Sig	
			Mean increase in annual cost per patient 2000 US$, inpatient and outpatient costs, based on the likelihood of increased Visual Field Defect Score (VFDS)**	**Group 2 vs Group 3: $**170 (£ 108) **Group 1 vs Group 3:** $ 247 (£ 156) **p value:** NR	
			Cost-effectiveness	NR	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rouland 2003 [125] France **Economic analysis:** Cost-effectiveness **Study design** decision analysis based on retrospective cohort study **Duration of follow up:** one year **Discount rates:** Costs: NA Effects: NA	**Patient group:** second-line adult patients with COAG or OHT (IOP>21 mmHg and no optic nerve damage) in at least one eye for whom treatment was changed or stopped, presenting in 37 centres in France. **<u>All patients</u>** **N:** 283 (549 eyes)* **N eyes with glaucoma:** 425 **Age (mean):** 65±1.5 **M/F:** 155/128 **Mean IOP at baseline:** 20.0±4.3 **<u>Group 1</u>** **N:** 209 eyes **Mean IOP at baseline:** 19.5±3.9 **<u>Group 2</u>** **N:** 90 eyes **Mean IOP at baseline:** 19.3±4.7 **<u>Group 3</u>** **N:** 39 eyes **Mean IOP at baseline:** 20.9±3.7	**Group 1:** Beta-blocker as a second-line treatment **Group 2:** Latanoprost as a second line treatment **Group 3:** Unfixed combination of Latanoprost+Timolol as a second line treatment	Mean IOP reduction per treated eye (mmHg)	**Group 1:** 2.1 **Group 2:** 3.0 **Group 3:** 5.3 **p value:** 0.02 (group 1 vs group 2 only)	**Funding:** Pharmacia corporation, Peapack, NJ, USA **Limitations:** Short follow-up Clinical outcomes were not compared to other studies and RCTs. **Additional outcomes:** average number of days remaining on the same treatment (longer for Group 2 and 3) **Notes:** * other groups treated with CAI and other combinations not reported here as a CEA was not performed ** calculated by NCC-AC from data reported in the study *** calculated by NCC-AC (different figures reported by authors)
			Proportion of eyes remaining on the same second-line treatment after 1 year	**Group 1:** 69% **Group 2:** 84% **Group 3:** 80% **p value:** 0.0068 (group 1 vs group 2 only)	
			Mean annual cost per patient** (2001, Euros direct costs: visits, medical procedures, drugs, surgery including trabeculectomy, trabeculoplasty, combined cataract-trabeculectomy, iridotomy, and 10% of cataract surgery) estimated from National Sources.	**Group 1:** € 179 (£ 124) **Group 2:** € 273 (£ 189) **Group 3:** € 329 (£ 228) **p value:** <0.0001 (group 1 vs group 2 only)	
			Cost-effectiveness*** additional cost per 1 mmHg of control gained after 1 year of treatment	Group 2 vs Group 1: £ 72 Group 3 vs Group 1: £33 Group 3 vs Group 2: £24	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Rouland 2005[126] France **Economic analysis:** cost-effectiveness **Study design:** decision analysis based on cohort study **Duration of follow-up:** 2 years **Discount rates:** Costs: NR Effects: NR	**Patient group:** second-line adult patients with COAG or OHT (IOP>21 mmHg and no optic nerve damage) in at least one eye presenting in 37 centres in France. **<u>All patients (eyes)</u>** **N:** 498 (672 eyes) **N eyes with glaucoma:** 511 **Age (mean±SD):** 64.8±12.9 **M/F:** 159/187 **Drop outs:** 152 **Mean IOP at baseline ±SD:** 20.1±4.1 **<u>Group 1</u>** **N eyes:** 248 eyes **Mean IOP**: 19.7 **<u>Group 2</u>** **N eyes:** 112 eyes **Mean IOP:** 19.9 **<u>Group 3</u>** **N eyes:** 39 eyes **Mean IOP:** 20.5	**Group 1:** Beta-blocker as a second-line treatment **Group 2:** Latanoprost as a second line treatment **Group 3:** Unfixed combination of Latanoprost+Timolol as a second line treatment	Frequency of episodes of adverse events	**Group 1:** 116 **Group 2:** 21 **Group 3:** 3 **p value:** NR	**Funding:** Pfizer **Limitations:** Short follow-up. Clinical outcomes were not compared to other studies and RCTs. **Additional outcomes:** average number of days remaining on the same treatment (longer for Group 2) **Notes:** * other groups include combinations, not reported here ** calculated by NCC-AC from data reported in the study *** calculated by NCC-AC
			Relative risk of adverse events vs group 1 (95% CI)	**Group 1:** 1.00 (0.996-1.004) **Group 2:** 0.40 (0.16-0.64) **Group 3:** NR **p value:** NR	
			Proportion of eyes remaining on the same second-line treatment after 2 years	**Group 1:** 41% **Group 2:** 62% **Group 3:** 44% **p value:** NR	
			Mean IOP reduction after 2 years per treated eye (mm Hg)	**Group 1**: 2.6 **Group 2**: 3.3 **Group 3**: 4.4 **p value**: NR	
			Mean 2-year cost per eye** (2003, Euros, direct costs: visits, medical procedures, drugs, surgery, 10% of cataract surgery)	**Group 1:** € 388 (£ 260) **Group 2:** € 556 (£ 373) **Group 3:** € 731 (£ 490) **p value:** NR	
			Cost-effectiveness*** additional cost per 1 mmHg of control gained after 2 years of treatment	Group 2 vs Group 1: £162 Group 3 vs Group 1: £128 Group 3 vs Group 2: £106	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Le Pen et al., 2005[82] France **Economic analysis:** Cost-utility **Study design** Decision analysis based on a Markov model **Time horizon:** 5 years **Discount rates:** Costs: 5% Effects: NR	**Patient group:** patients with advanced POAG in five European countries.	**Intervention 1:** Timolol 0.5% twice daily as first-line. **Intervention 2:** Latanoprost 0.005% once daily as first-line. **Intervention 3:** Travoprost 0.004% once daily as first-line.	Mean daily IOP over all visit days (mmHg)*	**Int 3 - Int 1:** -1.3 **Int 3- Int 2:** -1.0 **p value:** <0.0001	**Funding:** Alcon Laboratories Inc, USA. **Limitations:** Complicated third and fourth line strategies after disease progression were not considered. Limited time horizon. Clinical outcomes were not derived from a systematic search. Calculations of QALYs and ICUR were dubious. **Additional outcomes:** Same outcomes reported for other countries (Austria, France, Germany, and the Netherlands). The results were consistent across countries. **Notes:** * data from Netland 2001[110] ** Calculated from an algorithm that links IOP with VFD *** unclear calculation ****ICUR as reported in the study= €23,828 (£ 15,989)
			Time without a VFD=disease progression over 5 years (years)**	**Int 1:** 2.812 **Int 2:** 3.285 **Int 3:** 3.417 **p value:** NR	
			Patients experiencing a new visual field defect after 5 years of treatment**(%)	**Int 1:** 72.8% **Int 2:** 59.4% **Int 3:** 55.7% **p value:** NR	
			QALYs over 5 years***	**Int 1:** 3.6001 **Int 2:** 3.6164 **Int 3:** 3.6210 **p value:** NR	
			Mean cost per patient over 5 years in the UK 2003 Euro (€ 1.5 = £1). Cost of drugs, visits, surgery, laser, taken from national sources (UK GP Research Database and BNF)	**Int 1:** € 790 (£ 530) **Int 2:** € 1,041 (£ 698) **Int 3:** € 993 (£ 666) **p value:** NR	
			Cost-effectiveness ICUR = incremental cost per QALY gained (2003 €) calculated from difference in costs and QALYs as reported above****	Int 3 vs Int 1: €10,150 (£ 6,767) Latanoprost is dominated by Travoprost	
			Sensitivity analysis Probabilistic SA based on a Monte Carlo simulation (variables included were the cut-off value adopted for defining stability, the utility loss associated with a new VFD and the cost of a stable and progressive patient).	Probability ICUR Int 3 vs Int 1 <45,000€/QALY is 98.8%.	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Cottle & Begg, 1988[27] Canada **Economic analysis:** CEA **Study design** cohort study **Duration of follow-up:** 12 months (mean) **Discount rates:** Costs: NA Effects: NA	**Patient group:** consecutive patients with newly diagnosed, untreated POAG (IOP => 21 mmHg in at least one eye, glaucomatous visual field loss). **<u>All patients</u>** **N:** 71 (130 eyes) **N with glaucoma:** 71 **Age (mean ± SD):** 64 (±13.1) **M/F:** 34/37 **Drop outs:** 0 **Mean IOP at baseline (all eyes):** 28.7 (± 6.13) **Ethnic origin:** all white **<u>Group 1</u>** **N:** 85 eyes* **<u>Group 2</u>** **N:** 20 eyes* **<u>Group 3</u>** **N:** 10 eyes* **<u>Group 4</u>** **N:** 19 eyes* **<u>Group 5</u>** **N:** 8 eyes*	**Group 1:** Timolol 0.25% (Beta-blocker) **Group 2:** Timolol 0.5% (Beta-blocker) **Group 3:** Dipivefrine 0.1% (Sympathomimetic) **Group 4:** Pilocarpine 2.0% **Group 5:** Pilocarpine 1.0%	Number of eyes controlled in terms of satisfactory IOP	**Group 1:** 39 (46%) **Group 2:** 10 (50%) **Group 3:** 8 (80%) **Group 4:** 7 (37%) **Group 5:** 5 (62%) **p value:** NR	**Funding:** IMS, Inc., supplied the costs of the drugs. The study received a Grant 6610-1272-42 from the National Health Research and Development Program, Department of National Health and Welfare, Canada **Limitations:** Very small sample size. Some patients were included in more than 1 group. **Notes:** * the same eye could be included in more than one group when the treatment was changed **calculated by NCC based on monthly costs and on the assumption that treating both eyes has the same cost of treating 1eye (bottle is discarded anyway after 1month).
			Number of severe adverse reactions	**Group 1:** 9 (11%) **Group 2:** 0 (0%) **Group 3:** 2 (20%) **Group 4:** 2 (10%) **Group 5:** 1 (12%) **p value:** NR	
			Usefulness Quotient (number of patients whose condition was controlled with no severe adverse reaction divided by the number of patients who started on the treatment)	**Group 1:** 0.39 **Group 2:** 0.50 **Group 3:** 0.60 **Group 4:** 0.36 **Group 5:** 0.50 **p value:** Not Sig	
			Mean annual cost per eye treated** 1982 Can $, mean wholesale cost per bottle of drug, included the medication discarded during the study and the surplus remaining at the end.	**Group 1:** $42 (£17) **Group 2:** $50 (£21) **Group 3:** $29 (£12) **Group 4:** $13 (£5) **Group 5:** $12 (£5) **p value:** NR	
			Mean annual cost per eye treated if 54 BNF prices are used.	**Group 1:** £44 **Group 2:** £36 **Group 3:** £46 **Group 4:** £30 **Group 5:** £32	
			Cost-effectiveness ** incremental cost per year per additional patient controlled without side effects	Group 1 and 2 dominated by Group 3 and 5. Group 2 vs Group 1: $73 (£30)	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
			Cost-effectiveness** Incremental cost per year per additional patient controlled without side effects, calculated by NCC-AC using 54 BNF prices.	Group 1 dominated by 2. Group 3 vs Group 2: £10. Group 1 and 2 dominated by Group 5.	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Stewart et al., 2002[143] USA **Economic analysis:** cost-effectiveness **Study design** Retrospective cohort study **Duration of follow-up:** up to 12 months **Discount rates:** Costs: NA Effects: NA	**Patient group:** adult patients diagnosed with POAG or OHT in at least one eye previously prescribed a topical beta-blocker as monotherapy. **All patients** **N:** 148 (one eye from each subject) **Group 1** **N:** 37 **Age (mean):** 72.8 **M/F:** 16/21 **Mean IOP at baseline:** 20.9 **Ethnic origin:** 27 Caucasian, 10 Black **Group 2** **N:** 74 **Age (mean):** 75.2 **M/F:** 31/43 **Mean IOP at baseline:** 20.9 **Ethnic origin:** 42 Caucasian, 30 Black, 2 Hispanic **Group 3** **N:** 37 **Age (mean):** 76.4 **M/F:** 14/23 **Mean IOP at baseline:** 21.7 **Ethnic origin:** 24 Caucasian, 12 Black, 1 Hispanic	**Group 1:** Switch from Beta-blocker to Latanoprost monotherapy **Group 2:** Beta-blocker + adjunctive therapy with Latanoprost once daily **Group 3:** Beta-blocker + adjunctive therapy with Brimonidine twice daily	Number of patients with therapeutic success (IOP decreased by 2 mm Hg or more)	**Group 1:** 54% (20/37) **Group 2:** 70% (52/74) **Group 3:** 49% (18/37) **p value:** 0.056	**Funding:** NR **Limitations:** Short follow-up. Retrospective study: possible selection bias. **Additional outcomes:** Treatment changes; number of visits; adverse events; difference in cost from beta-blockers to post-enrolment treatment. **Notes:** *calculated by NCC based on monthly cost
			Mean IOP change from baseline to final follow-up visit (% change in IOP)	**Group 1:** 2.8 (13.4%) **Group 2:** 4.5 (21.5%) **Group 3:** 4.6 (21.2%) **p value:** 0.23 (on mean IOP change)	
			Mean annual cost per patient* 2001, US$ Average wholesale prices of medicines prescribed and reimbursement cost of visits and tests due to adverse events	**Group 1:** $644 (£401) **Group 2:** $998 (£622) **Group 3:** $1,274 (£794) **p value:** 0.038 (for monthly cost)	
			Cost-effectiveness* additional cost per 1 mmHg of change in IOP after 1 year of treatment	On the basis of %change in IOP Group 3 is dominated by Group 2. Group 2 vs Group 1: $208 (£130)	
			Sensitivity analysis	NR	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Ainsworth & Jay, 1991[3] UK **Economic analysis:** cost analysis **Study design** RCT* **Duration of follow-up:** 8 years **Discount rates:** Costs: none Effects: none	**Patient group:** consecutive patients of 8 ophthalmologists in 5 hospitals in Glasgow area newly diagnosed with POAG (untreated IOP of at least 26 mmHg on two occasions and field defect characteristics). **<u>All patients</u>** **N:** 104 **<u>Group 1</u>** **N:** 51 (23 unilateral glaucoma) **<u>Group 2</u>** **N:** 53 (23 unilateral glaucoma)	**Group 1:** Early trabeculectomy (within 4 weeks of diagnosis). Preliminary medical therapy is used if necessary to reduce the IOP to a safe level prior to surgery. **Group 2:** Conventional management: up to a maximum of three different topical or systemic drugs and late trabeculectomy if medical therapy has failed.	**Mean cost per patient (unilateral** – bilateral glaucoma)** 1989 GBP, cost of drugs plus 6% pharmacists' prescription fee, outpatient visits, field tests, inpatient stay***, operation. Costs adjusted for mortality.	**Group 1:** £2,139 - £2,560 **Group 2:** £1,920 - £2,569 **p value:** NR	**Funding:** NR **Limitations:** Population description missing. Hospital length of stay after surgery could have decreased since time of study. **Notes:** *From Jay1988[65].In Jay 1988 fewer patients. ** Cost of unilateral glaucoma includes subsequent treatment of the fellow eye if applicable. ***average length of stay=7.6 days
			Cost-effectiveness	NR	
			Sensitivity analysis	When the length of inpatient admission is reduced to 4 days or 1 day, early trabeculectomy becomes the less costly strategy. 4 days: Group 1 £1,780 Group 2 £ 1,875 1 day: Group 1 £ 1,130 Group 2 £ 1,405	

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Henson et al., 2003[60] UK **Economic analysis:** cost analysis **Study design** comparative study with historical control **Duration of follow-up:** 3 years **Discount rates:** Costs: NR Effects: NA	**Patient group:** suspect of having glaucoma **Group 1** **N:** 194 **Group 2** **N:** 93	**Group 1:** Patients referred to a group of accredited optometrists working within their own practices and subsequently referred to Manchester Royal Eye Hospital if meeting referral criteria. **Group 2:** Patients referred to the GP and then to Manchester Royal Eye Hospital	**3-year cost of overall scheme** 2001 GBP training of optometrists, fees to optometrist, audit, minus cost savings from non-referred cases (40%) to hospital and GP	**Group 2 - Group 1:** 13,426 **p value:** NR	**Funding:** Manchester Health Authority **Limitations:** Cost of false negatives was not accounted for. **Additional outcomes:** if 23 patients per month are enrolled in the scheme of group 1, the cost saving is approximately £16 per patient.

Economic Evidence (continued)

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
Coast 1997[23] UK **Economic analysis:** Cost Analysis **Study design** RCT[52,140,142] **Perspective:** NHS and patients **Duration of follow-up:** 1 year **Discount rates:** Costs: NA Effects: NA	**Patient group:** patients with glaucoma whose IOP was satisfactorily controlled with treatment; Snellen VA of 6/18 or better in both eyes, aged 50 or above **<u>All patients</u>** **N:** 405 **Drop-outs:** 2 **<u>Group 1</u>** **N:** 204 **Drop-outs:** 9 **<u>Group 2</u>** **N:** 201 **Drop-outs:** 4	**Group 1:** Monitoring by ophthalmologists with a 10-month interval **Group 2:** Monitoring by optometrists, with a 6-month interval and referral to hospital when necessary.	**Cost per glaucoma visit** 1994 GBP Cost of staff, consumables, overheads.	**Group 1:** 50 **Group 2:** 29 **p value:** NR	**Funding:** South and West Research and Development Directorate, Avon Health and the International Glaucoma Association. **Limitations:** Optometrists were volunteers, therefore the findings cannot be generalised. Effectiveness was not estimated. Data on patients are missing. **Additional outcomes:** 46 clinics per annum could be saved from a total of 1200 clinics. Time and costs to the patients were lower in Group 2.
			Annual full cost per patient 1994 GBP Cost of staff, training of optometrists, consumables, referrals from optometrists (19% patients), and overheads.	**Group 1:** 60 **Group 2:** *77* **p value:** NR	
			Marginal annual opportunity cost per patient 1994 GBP. Cost of staff time.	**Group 1:** £15 **Group 2:** £25 **p value:** NR	
			Cost-effectiveness	NA	
			Sensitivity analysis	When time spent by optometrists with patients was 60 minutes rather than 35 minutes, the annual cost per patient was £124 When rate of referrals in group 2 was 50% lower or higher than baseline annual cost per patient in group 2 was respectively £68 and £87. When follow up interval in group 2 was similar to group 1, the annual cost per patient in group 2 was £46. If the caseload optometrists are willing to accept is 100 patients, the marginal opportunity cost per patient becomes £45.	

Appendix E

Forest plots

Figure 1 Any treatment vs. no treatment – OHT conversion to COAG & COAG progression

Review: Glaucoma - Treatments
Comparison: 61 Any and all treatments v NT/Placebo
Outcome: 05 Number of patients with conversion to or progression of glaucoma - subgrouped by condition

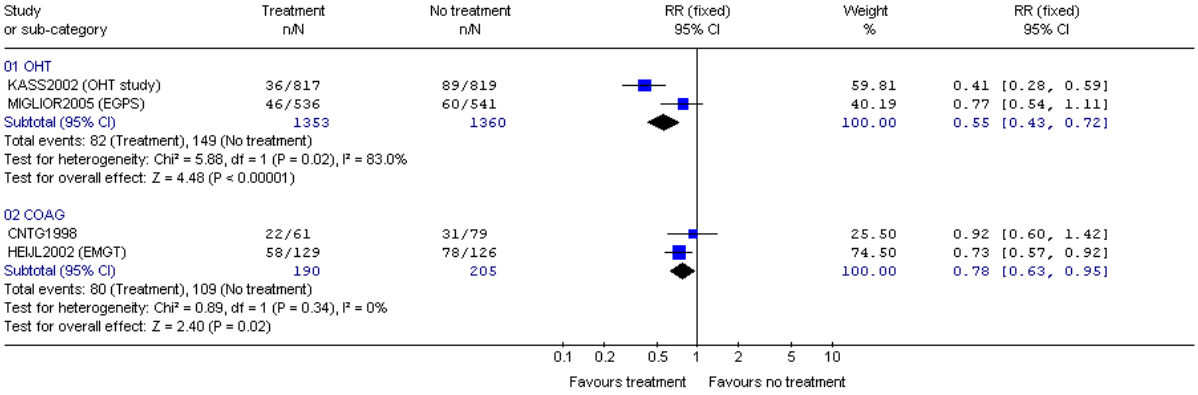


Figure 2 Any treatment vs. no treatment – visual field progression in OHT and COAG patients

Review: Glaucoma - Treatments
Comparison: 61 Any and all treatments v NT/Placebo
Outcome: 07 Number of patients with visual field progression subgrouped by condition

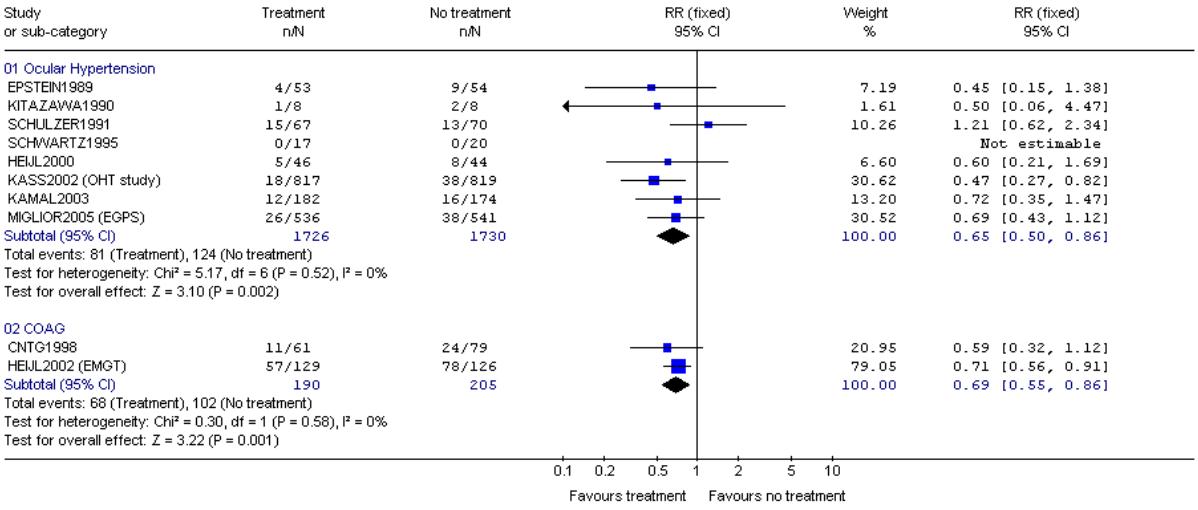


Figure 3 Any treatment vs. no treatment – change in IOP from baseline

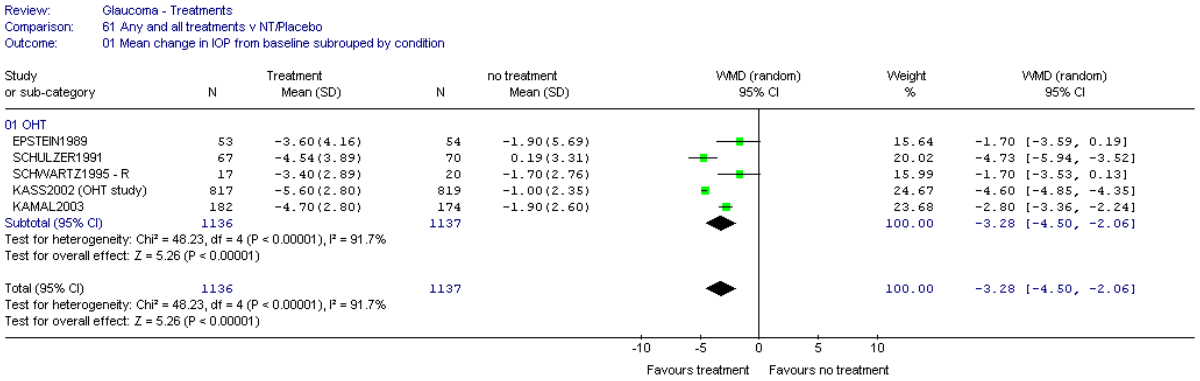


Figure 4 Beta-blockers vs. no treatment – visual field progression

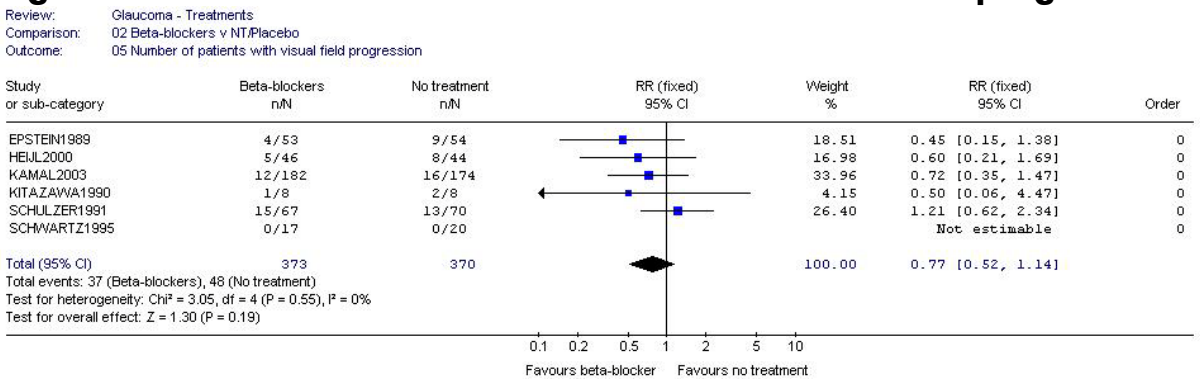


Figure 5 Beta-blockers vs. no treatment – change in IOP from baseline

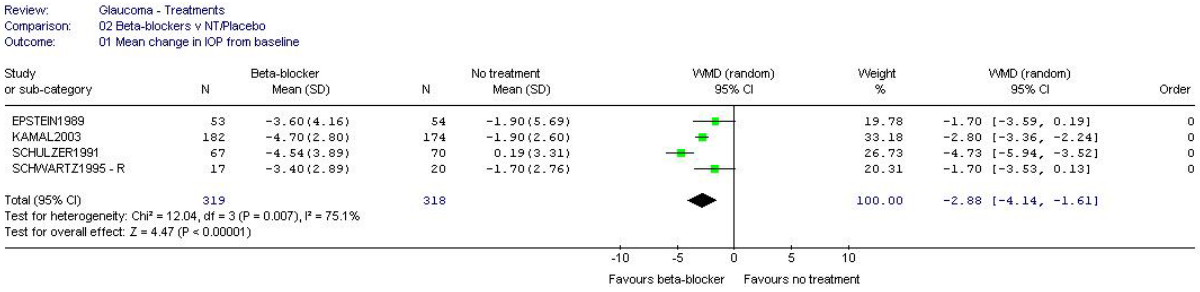


Figure 6 Beta-blockers vs. no treatment – number of patients with an IOP > 30mmHg

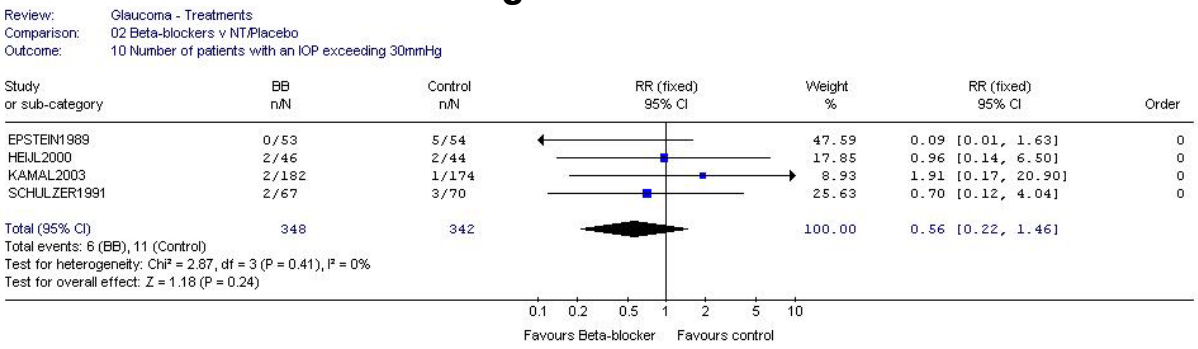


Figure 7 Beta-blockers vs. no treatment – adverse events: respiratory

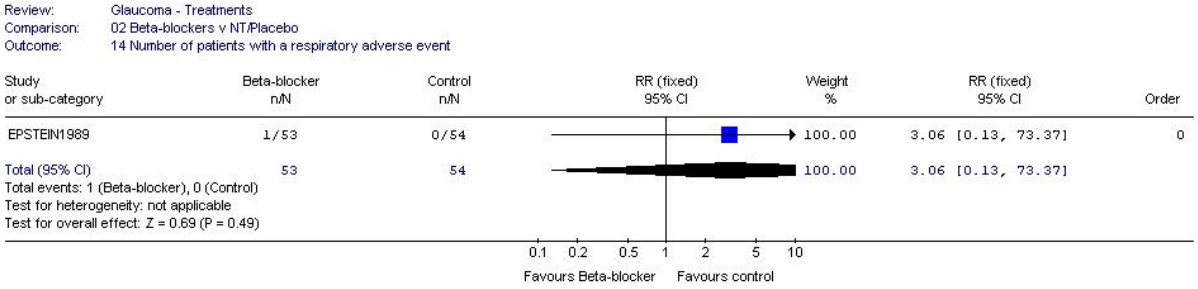


Figure 8 Beta-blockers vs. no treatment – adverse events: cardiovascular

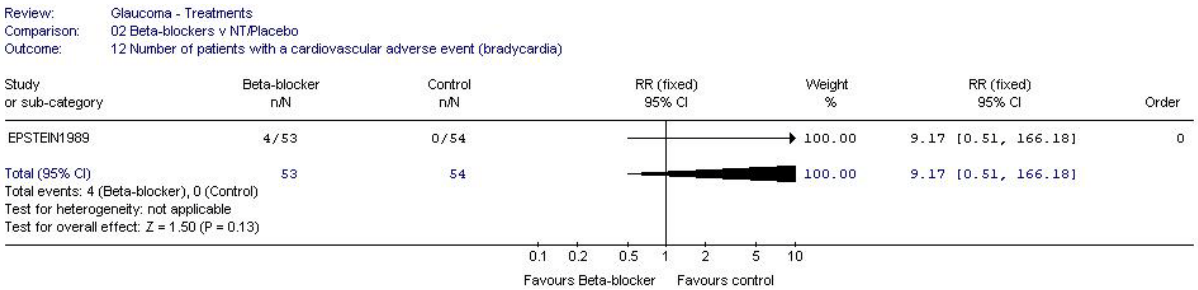


Figure 9 Beta-blockers dosage – timolol 0.5% vs. timolol 0.25% – change in IOP from baseline

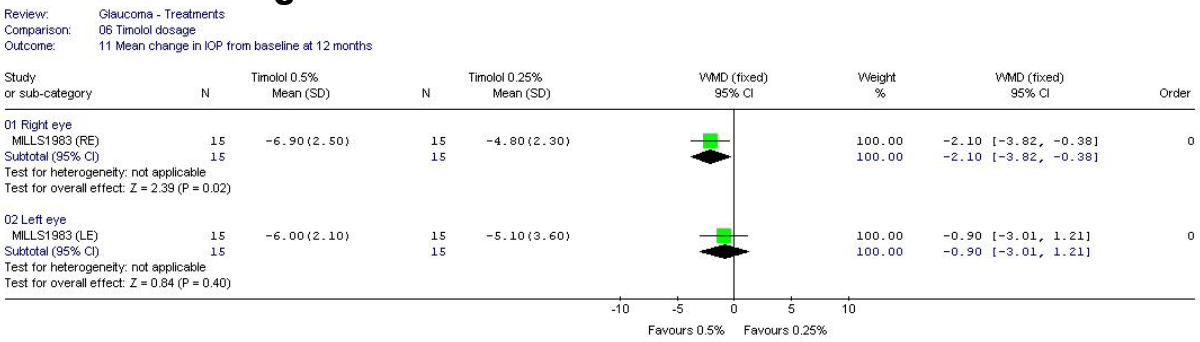


Figure 10 Prostaglandins vs. beta-blockers – change in IOP from baseline

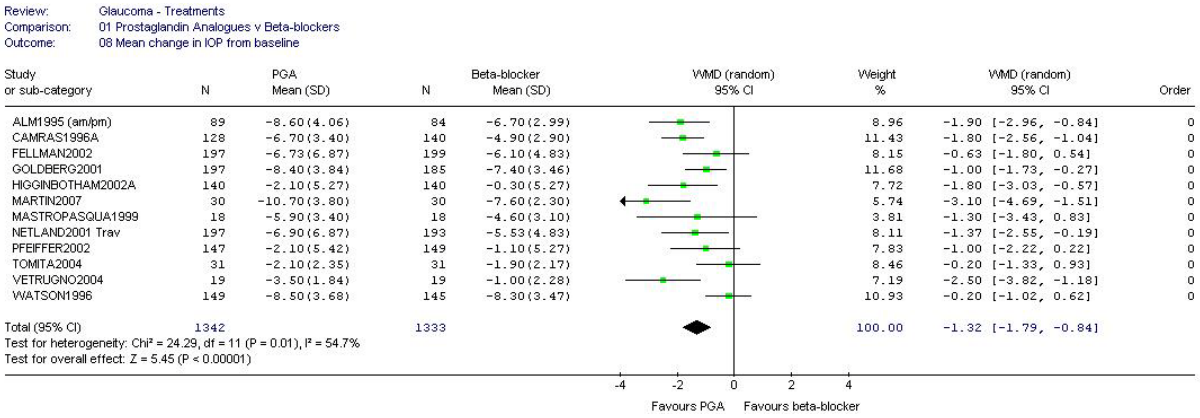


Figure 11 Prostaglandins vs. beta-blockers – number of patients with acceptable IOP

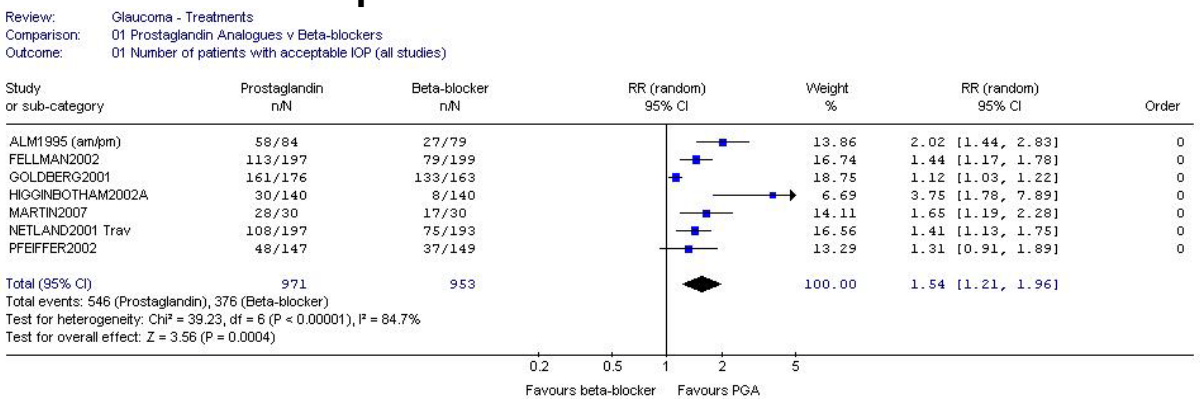


Figure 12 Prostaglandins vs. beta-blockers – adverse events: respiratory

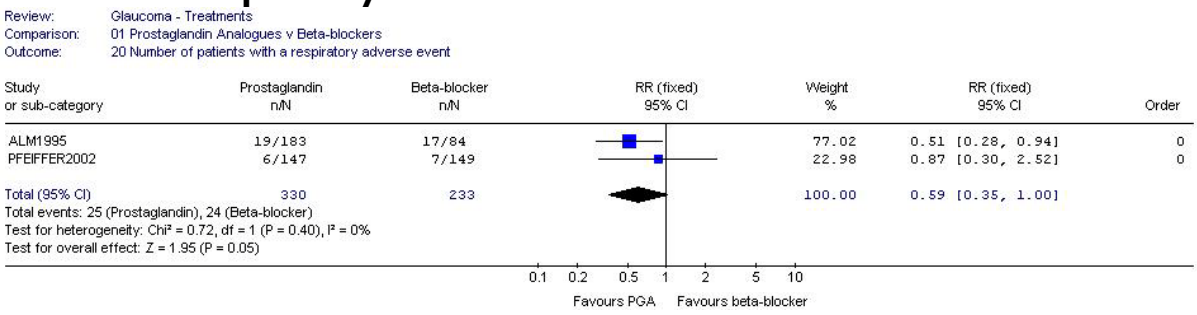


Figure 13 Prostaglandins vs. beta-blockers – adverse events: cardiovascular

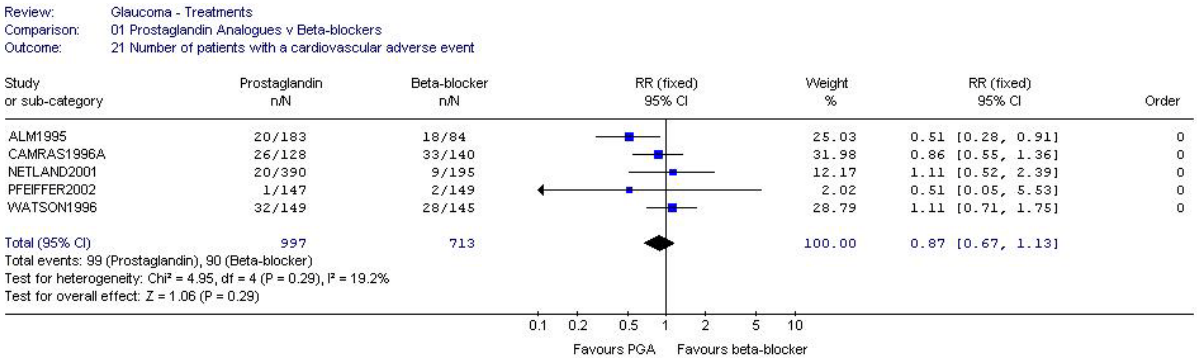


Figure 14 Prostaglandins vs. beta-blockers – adverse events: allergic reaction

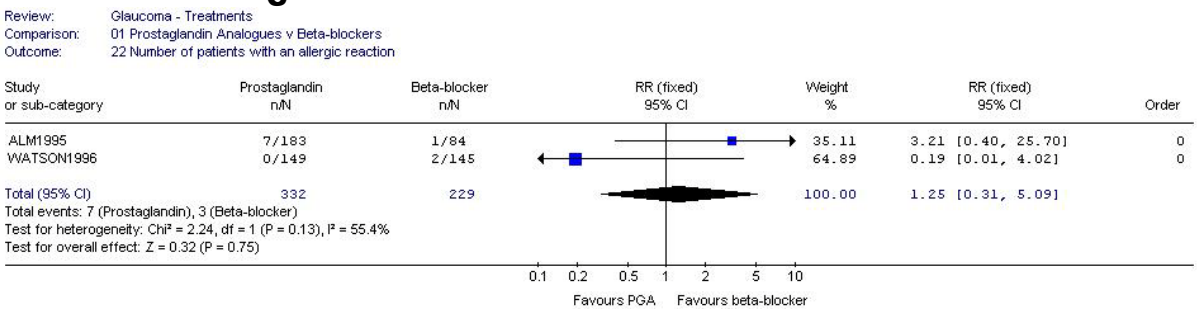


Figure 15 Prostaglandins vs. beta-blockers – adverse events: hyperaemia

Review: Glaucoma - Treatments
Comparison: 01 Prostaglandin Analogues v Beta-blockers
Outcome: 23 Number of patients with hyperaemia

Study or sub-category	Prostaglandin n/N	Beta-blocker n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
CAMRAS1996A	7/128	3/140		2.22	2.55 [0.67, 9.66]	0
COHEN2004A	23/167	2/163		1.57	11.22 [2.69, 46.84]	0
FELLMAN2002	87/201	18/202		13.92	4.86 [3.04, 7.76]	0
GOLDBERG2001	64/197	13/186		10.37	4.65 [2.65, 8.15]	0
HIGGINBOTHAM2002	212/474	32/241		32.90	3.37 [2.40, 4.72]	0
MARTIN2007	4/30	0/30		0.39	9.00 [0.51, 160.17]	0
MASTROPASQUA1999	5/17	3/17		2.33	1.67 [0.47, 5.90]	0
NETLAND2001	153/396	28/200		28.85	2.76 [1.92, 3.98]	0
VETRUGNO2004	5/19	0/19		0.39	11.00 [0.65, 186.02]	0
WATSON1996	22/149	9/145		7.07	2.38 [1.13, 4.99]	0
Total (95% CI)	1778	1343		100.00	3.58 [2.97, 4.32]	

Total events: 582 (Prostaglandin), 108 (Beta-blocker)
Test for heterogeneity: Chi² = 10.82, df = 9 (P = 0.29), I² = 16.8%
Test for overall effect: Z = 13.27 (P < 0.00001)

Figure 16 Prostaglandins vs. sympathomimetics – change in IOP from baseline

Review: Glaucoma - Treatments
Comparison: 07 Prostaglandin Analogues v Sympathomimetics
Outcome: 01 Mean change in IOP from baseline

Study or sub-category	PGA N	PGA Mean (SD)	Sympathomimetic N	Sympathomimetic Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI	Order
CAMRAS2005	150	-5.70(3.22)	151	-3.10(3.69)		46.20	-2.60 [-3.38, -1.82]	0
KAMPIK2002	187	-7.10(3.30)	192	-5.20(3.50)		53.80	-1.90 [-2.58, -1.22]	0
Total (95% CI)	337		343			100.00	-2.22 [-2.91, -1.54]	

Test for heterogeneity: Chi² = 1.74, df = 1 (P = 0.19), I² = 42.6%
Test for overall effect: Z = 6.37 (P < 0.00001)

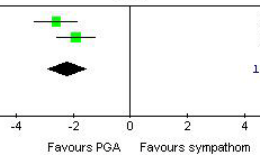


Figure 17 Prostaglandins vs. sympathomimetics – adverse events: allergic reaction

Review: Glaucoma - Treatments
Comparison: 07 Prostaglandin Analogues v Sympathomimetics
Outcome: 10 Number of patients with an allergic reaction

Study or sub-category	Prostaglandin n/N	Sympathomimetic n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Order
KAMPIK2002	0/187	16/188		100.00	0.03 [0.00, 0.50]	0
Total (95% CI)	187	188		100.00	0.03 [0.00, 0.50]	

Total events: 0 (Prostaglandin), 16 (Sympathomimetic)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.44 (P = 0.01)

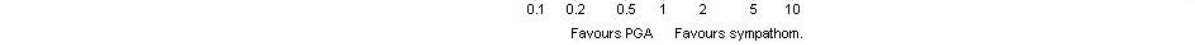


Figure 18 Prostaglandins vs. sympathomimetics – adverse events: hyperaemia

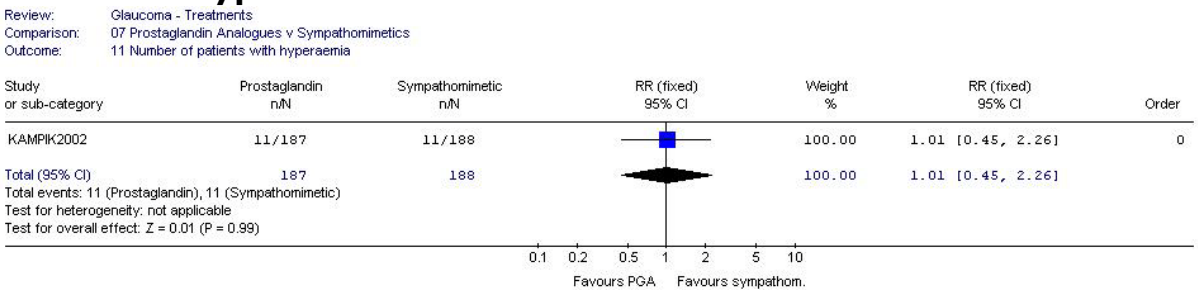


Figure 19 Carbonic anhydrase inhibitors vs. no treatment – conversion to COAG

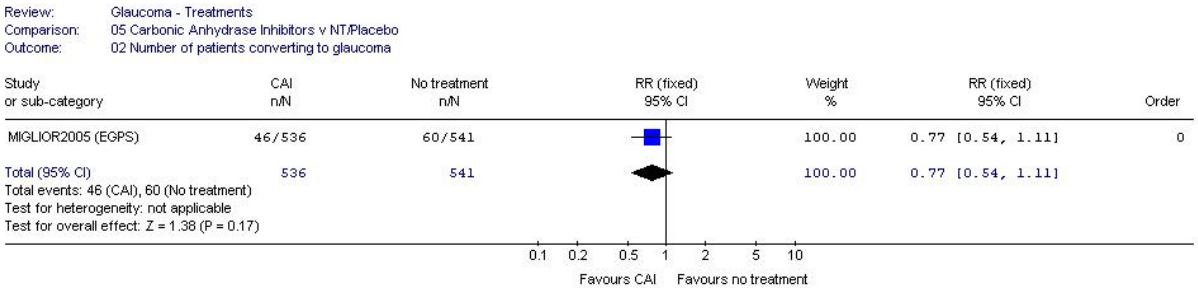


Figure 20 Carbonic anhydrase inhibitors vs. no treatment – visual field progression

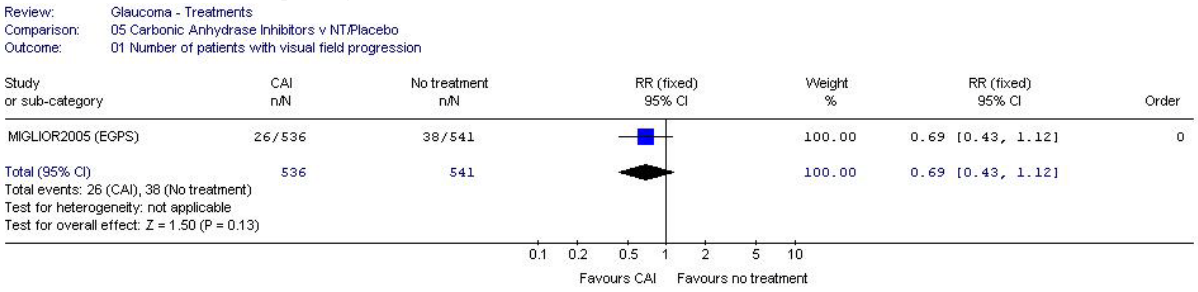


Figure 21 Carbonic anhydrase inhibitors vs. no treatment – number of patients with an IOP > 35mmHg

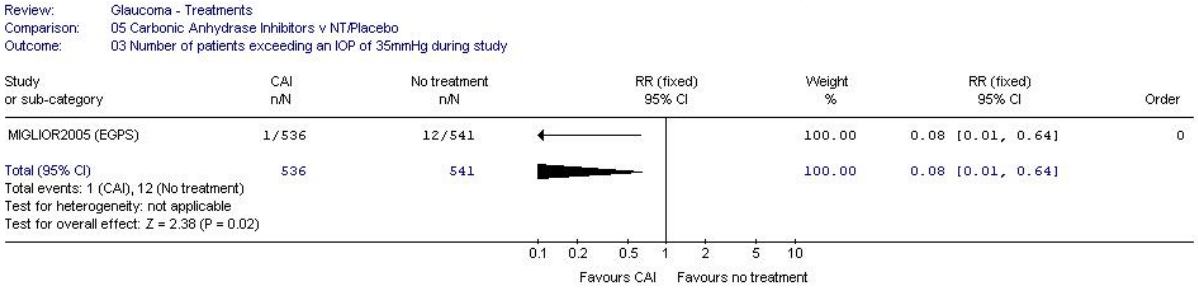


Figure 22 Carbonic anhydrase inhibitors vs. beta-blockers – adverse events: hyperaemia

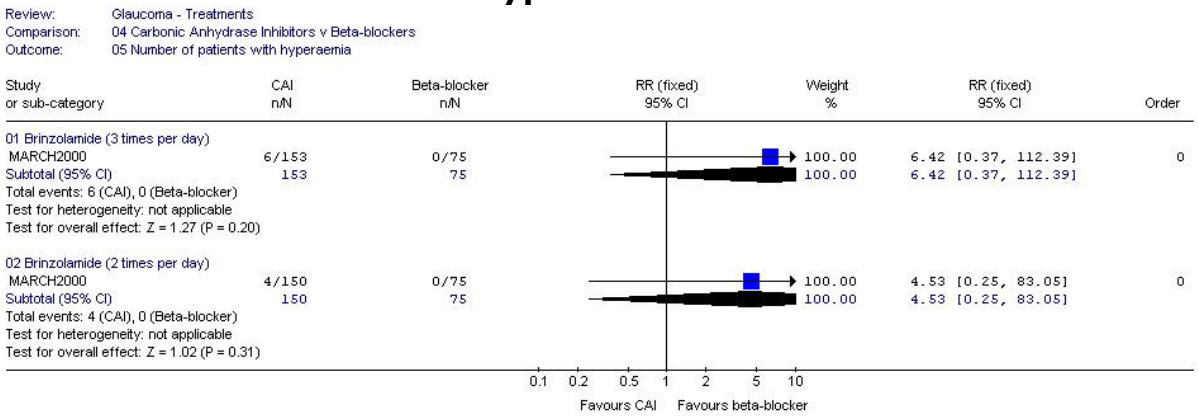


Figure 23 Sympathomimetics vs. beta-blockers – visual field progression

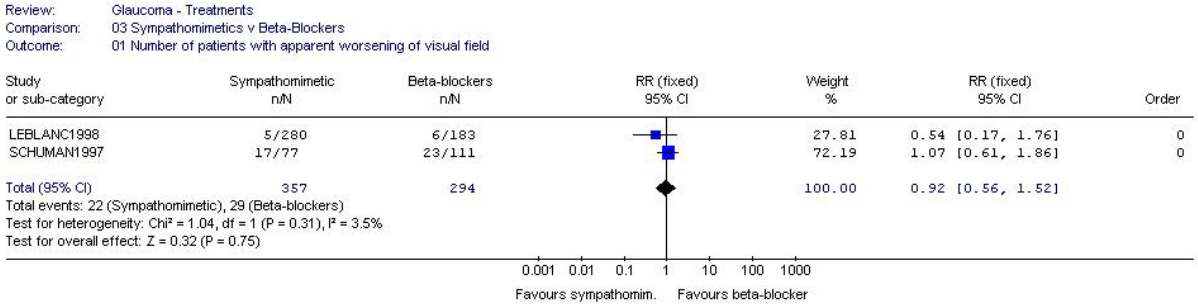


Figure 24 Sympathomimetics vs. beta-blockers – change in IOP from baseline

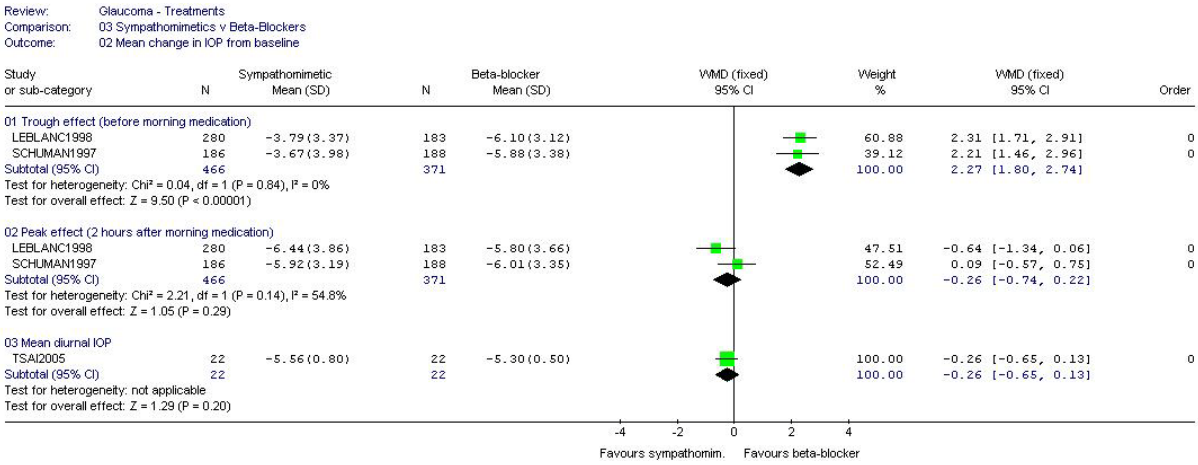


Figure 25 Sympathomimetics vs. beta-blockers – adverse events: allergic reaction

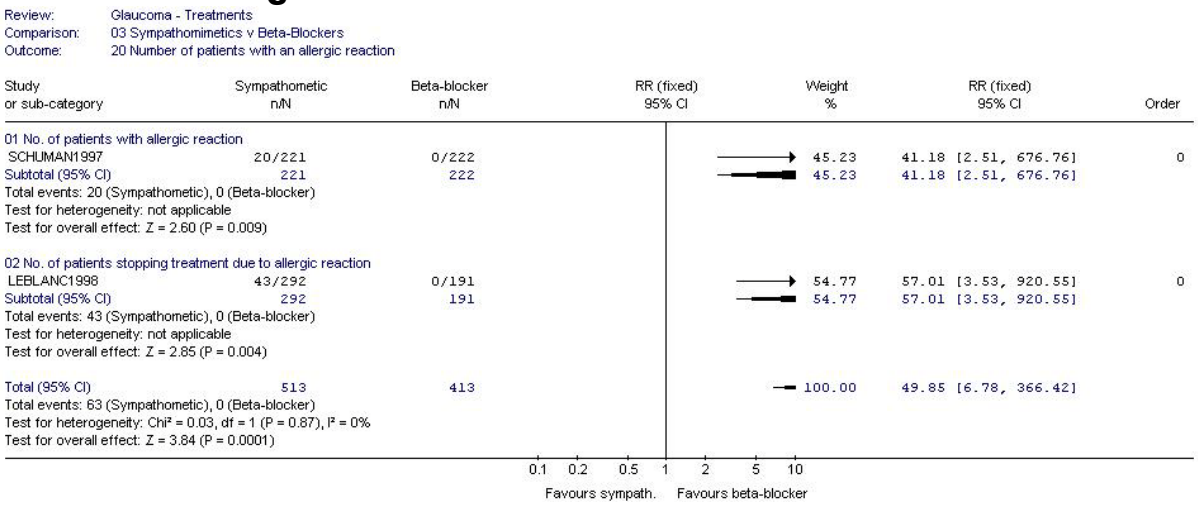


Figure 26 Sympathomimetics vs. beta-blockers – adverse events: fatigue/drowsiness

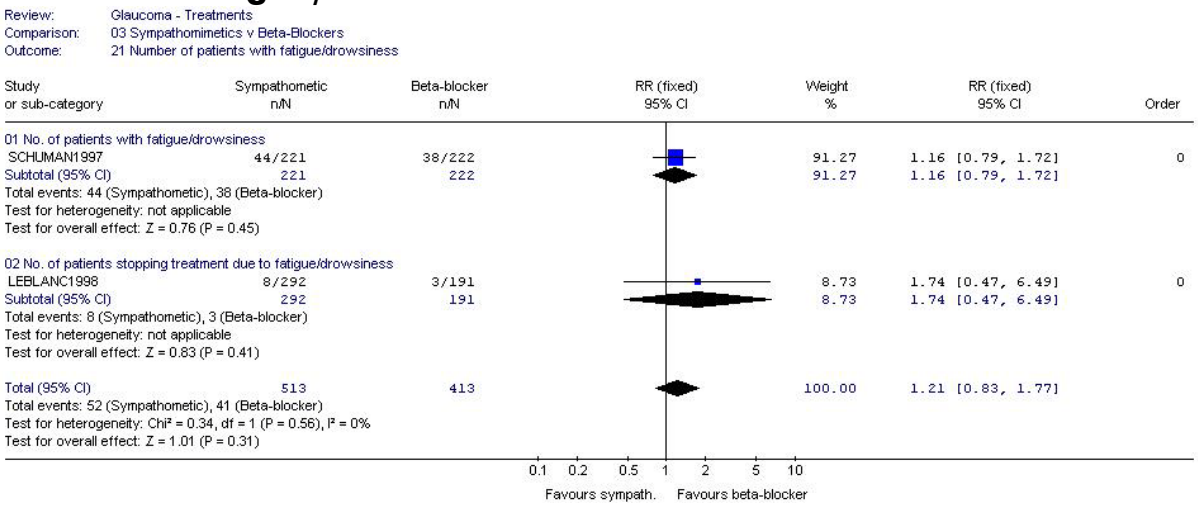
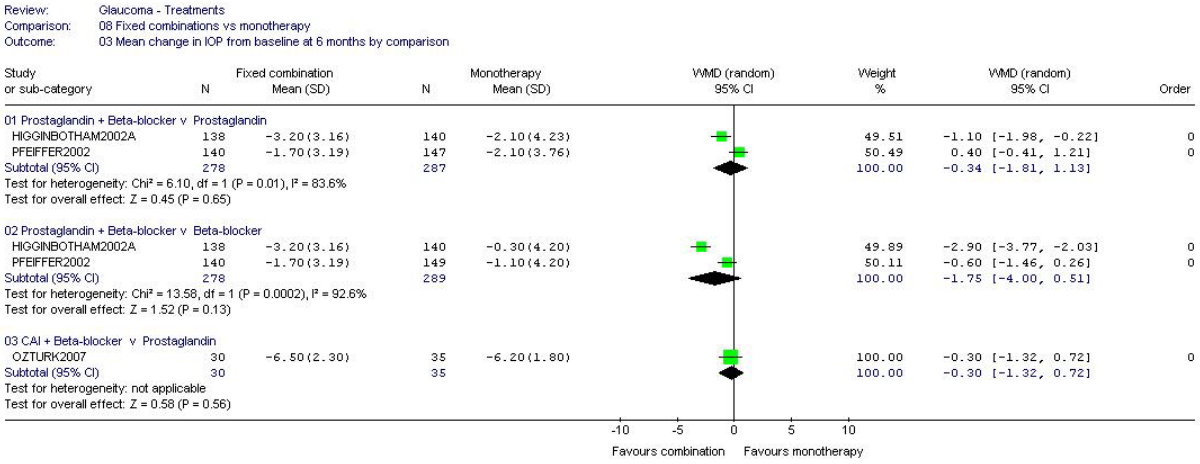
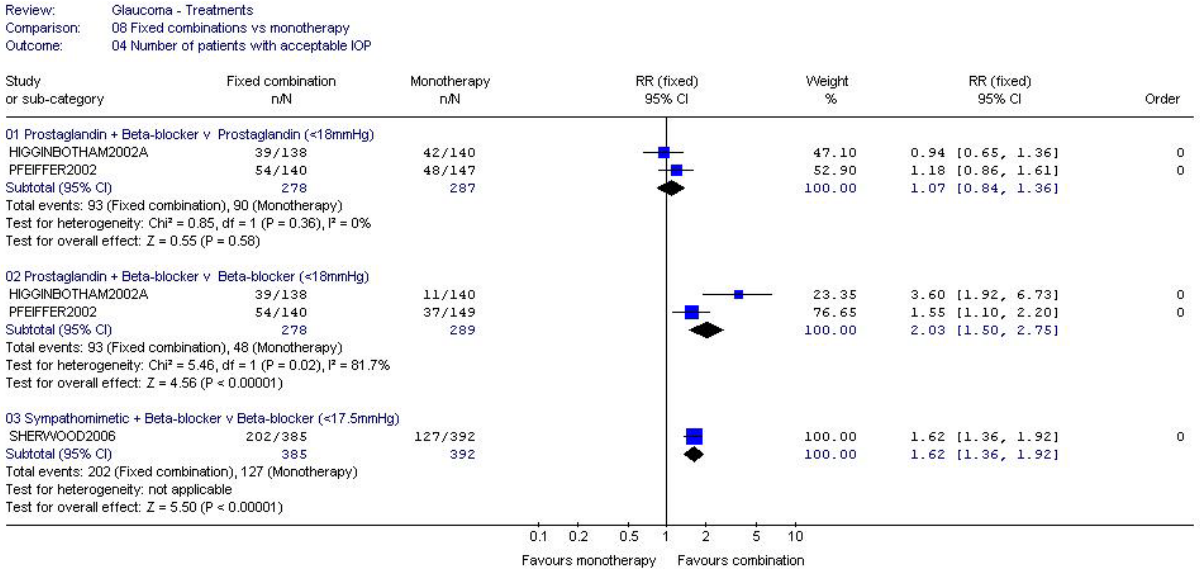


Figure 27 Fixed combination vs. single medications – change in IOP from baseline *



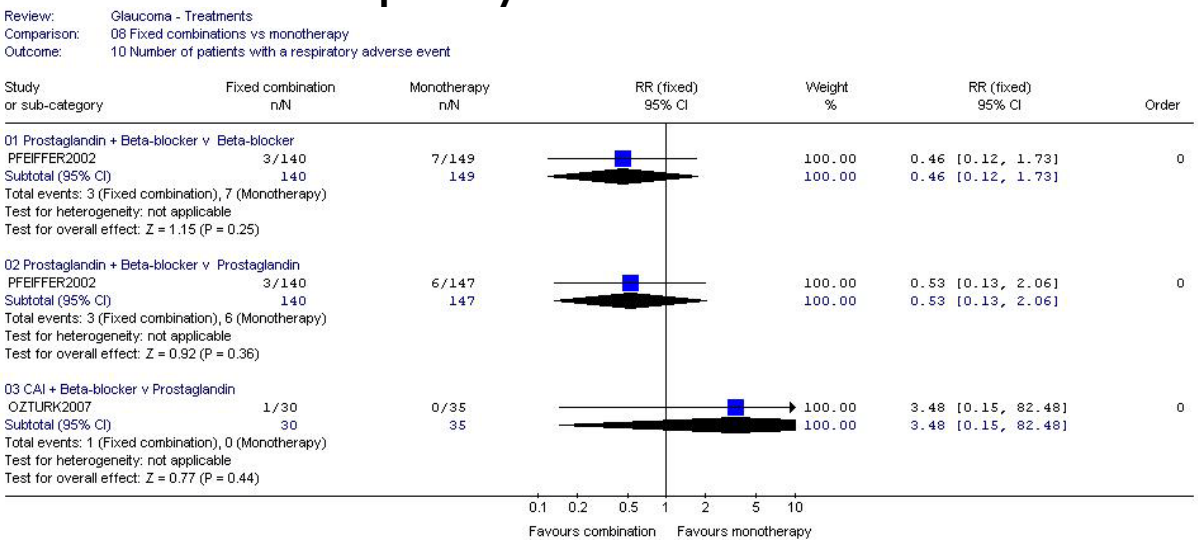
**Although all drug combinations for fixed preparations are presented in one forest plot the effect size is not totaled and each comparison is considered separately*

Figure 28 Fixed combination vs. single medications – number of patients with an acceptable IOP *



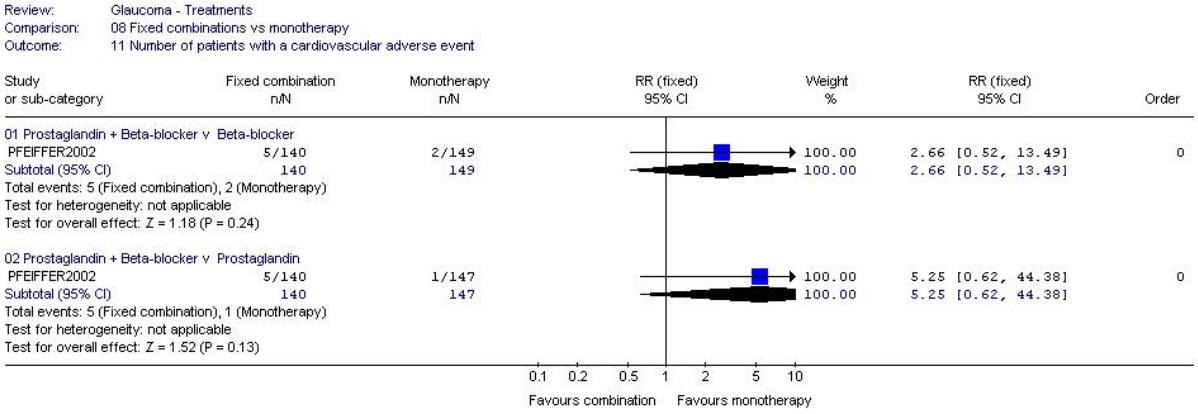
**Although all drug combinations for fixed preparations are presented in one forest plot the effect size is not totaled and each comparison is considered separately*

Figure 29 Fixed combination vs. single medications – adverse events: respiratory *



**Although all drug combinations for fixed preparations are presented in one forest plot the effect size is not totaled and each comparison is considered separately*

Figure 30 Fixed combination vs. single medications – adverse events: cardiovascular *



**Although all drug combinations for fixed preparations are presented in one forest plot the effect size is not totaled and each comparison is considered separately*

Figure 31 Fixed combination vs. single medications – adverse events: allergic reaction *

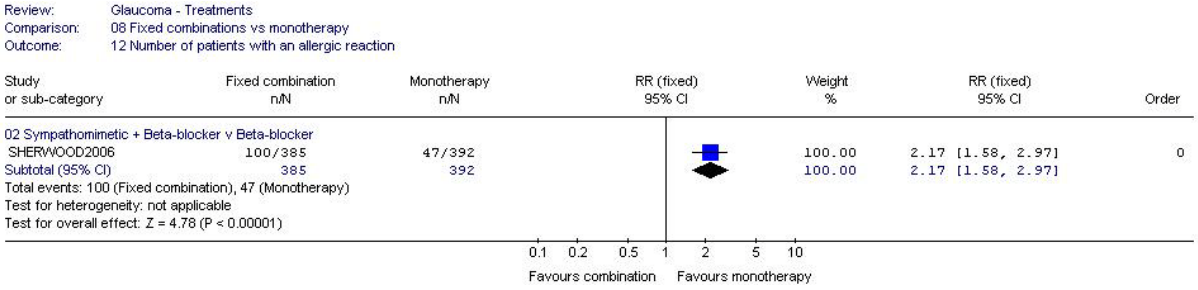
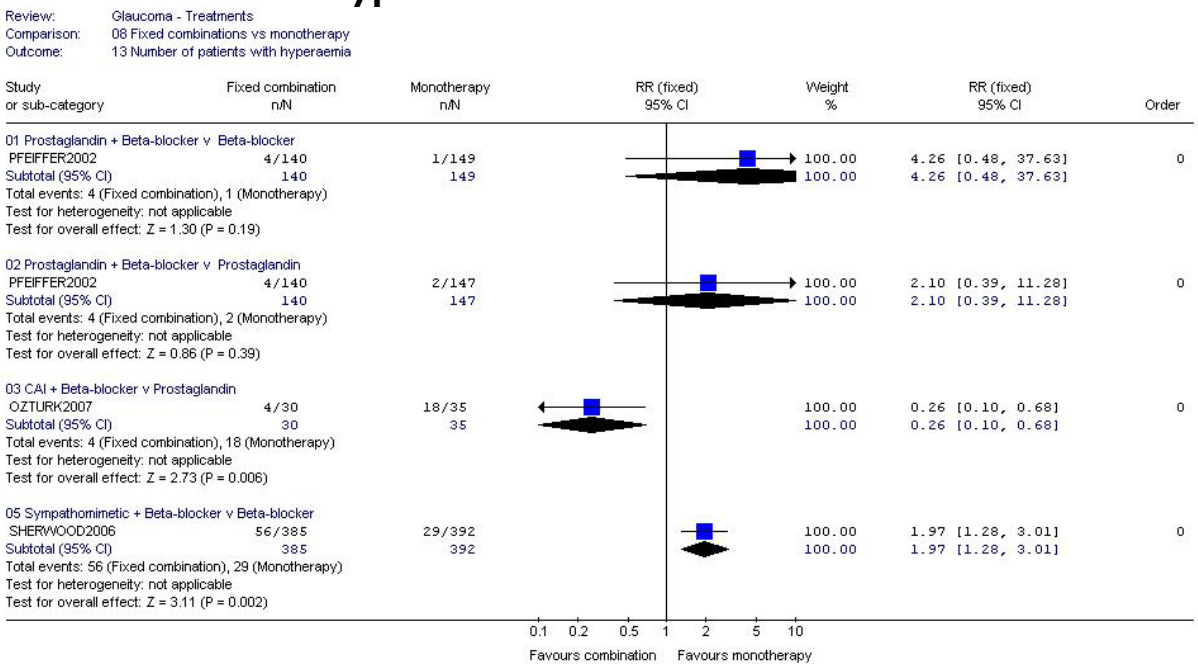


Figure 32 Fixed combination vs. single medications – adverse events: hyperaemia



**Although all drug combinations for fixed preparations are presented in one forest plot the effect size is not totaled and each comparison is considered separately*

Figure 33 Separate combination vs. single medications – change in IOP from baseline

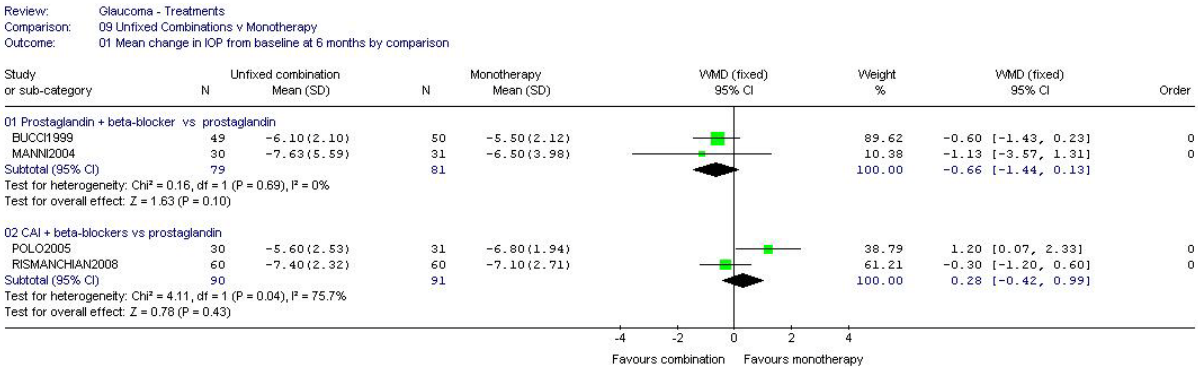


Figure 34 Separate combination vs. single medications – number of patients with an acceptable IOP

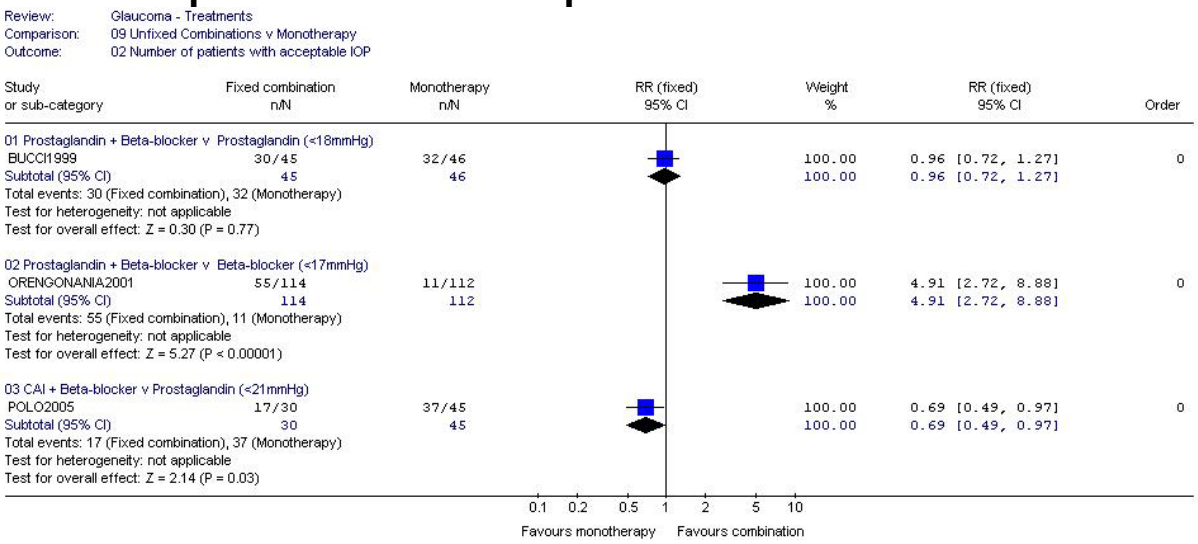


Figure 35 Separate combination vs. single medications – adverse events: respiratory

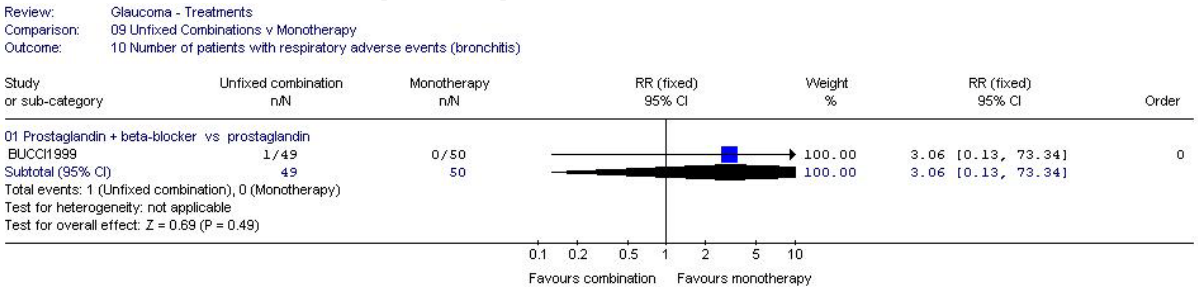


Figure 36 Separate combination vs. single medications – adverse events: hyperaemia

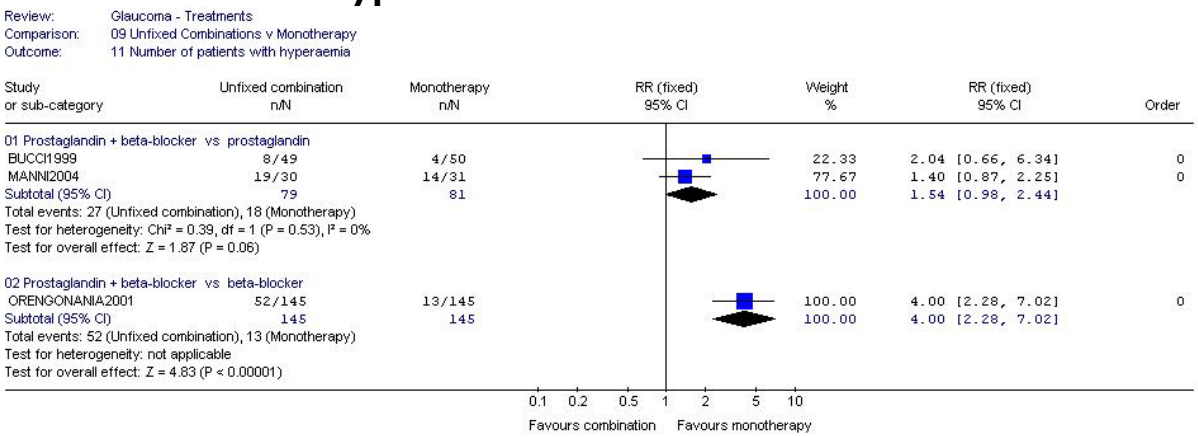


Figure 37 Selective laser trabeculoplasty vs. argon laser trabeculoplasty – change in IOP from baseline

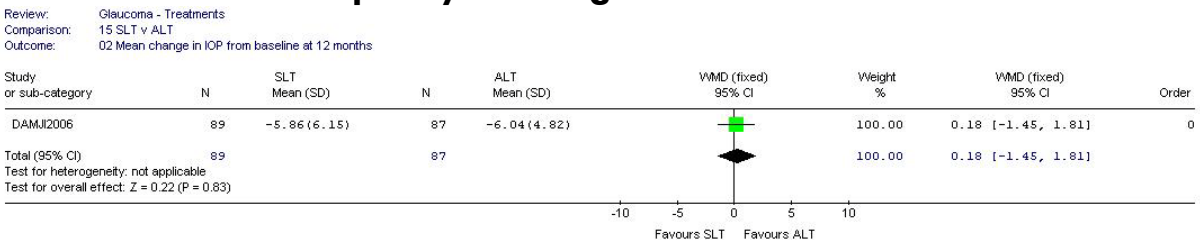


Figure 38 Selective laser trabeculoplasty vs. argon laser trabeculoplasty – unacceptable IOP

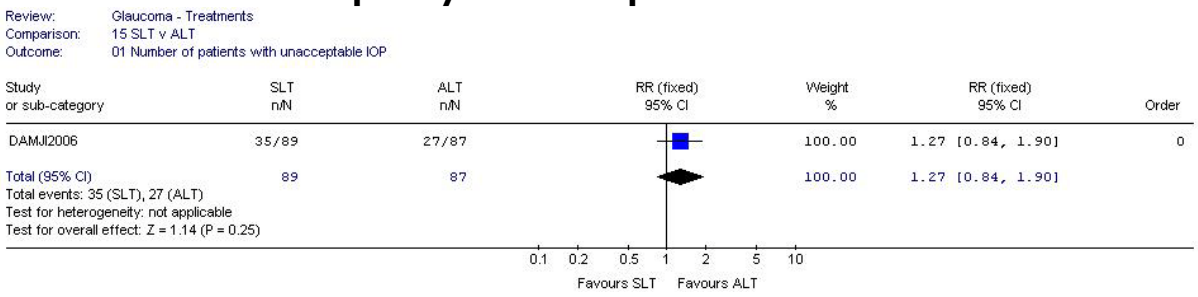


Figure 39 Selective laser trabeculoplasty vs. argon laser trabeculoplasty – complications: PAS formation

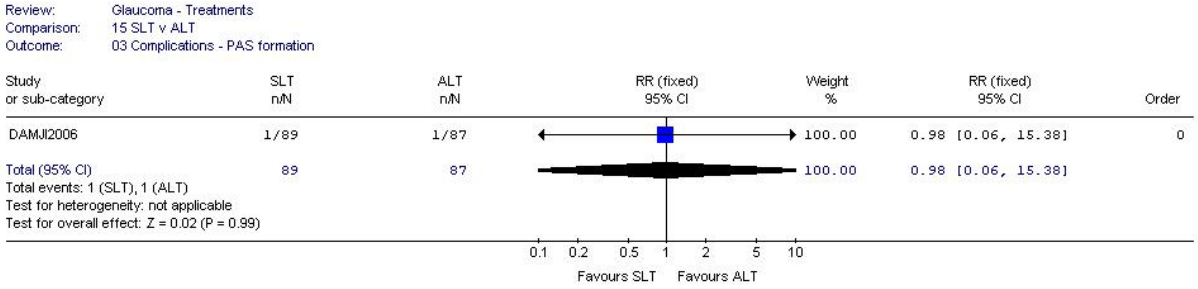


Figure 40 Laser vs. pharmacological treatment – unacceptable IOP

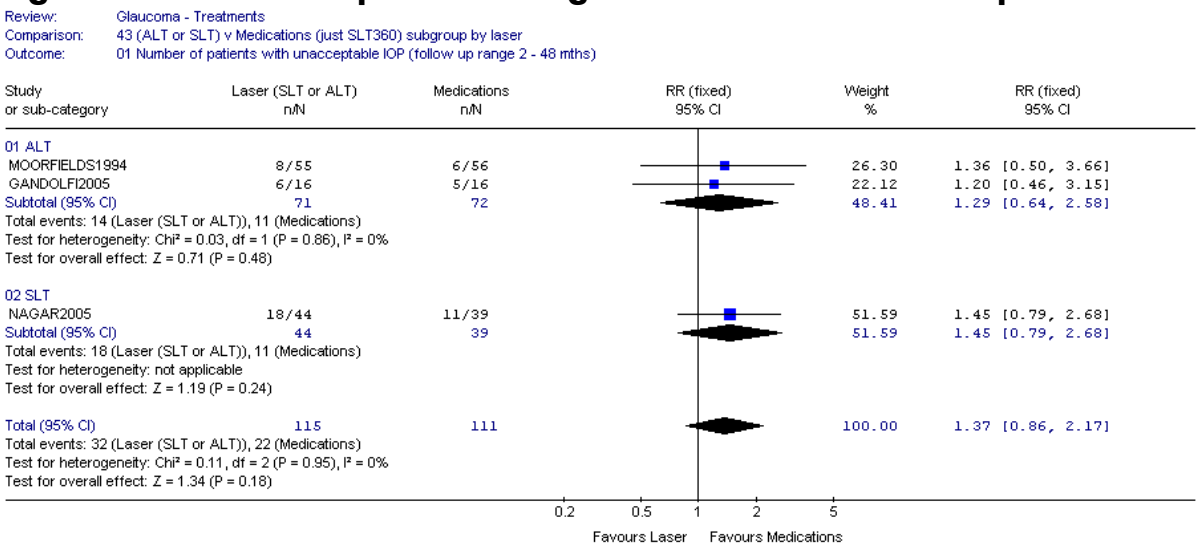


Figure 41 Laser plus pharmacological treatment vs. pharmacological treatment – unacceptable IOP

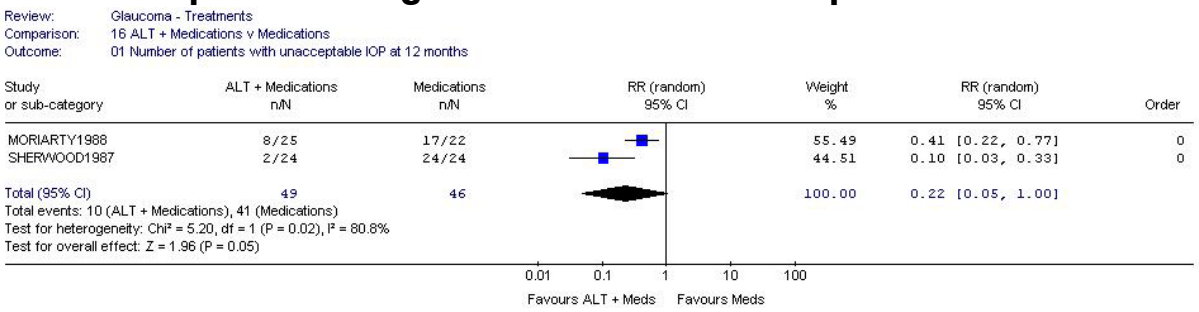


Figure 42 Laser vs. trabeculectomy – unacceptable IOP

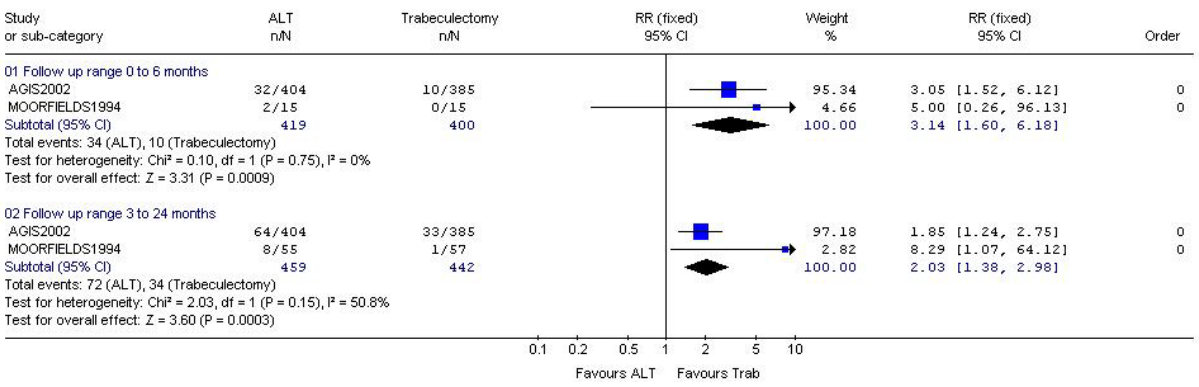


Figure 43 Trabeculectomy vs. pharmacological treatment – visual field progression at 1-5 yrs

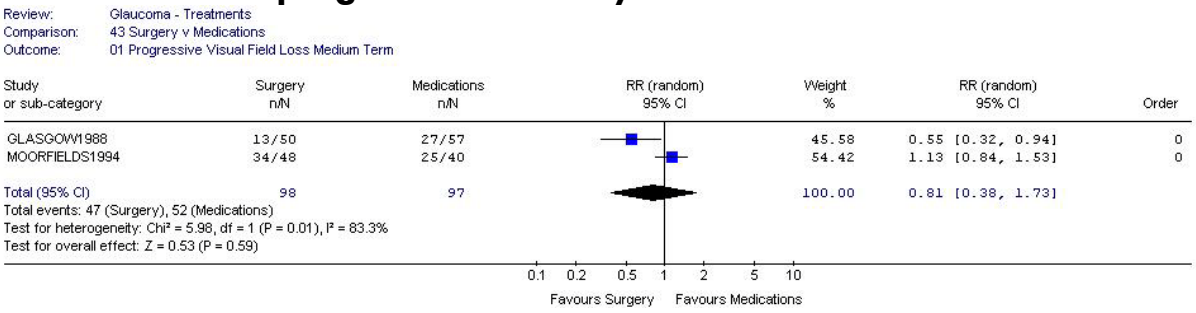


Figure 44 Trabeculectomy vs. pharmacological treatment – change in IOP from baseline at 12 mths

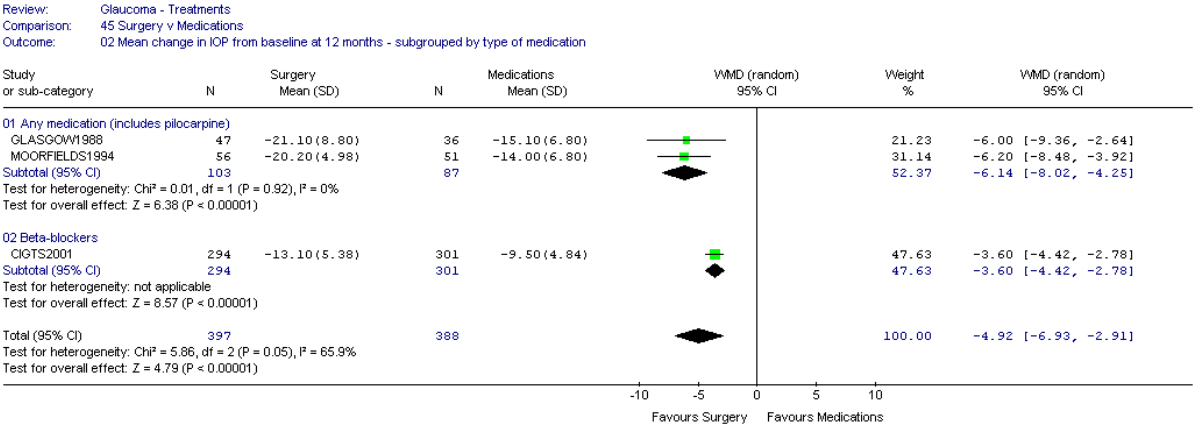


Figure 45 Trabeculectomy vs. pharmacological treatment – change in IOP from baseline at 1-5 yrs

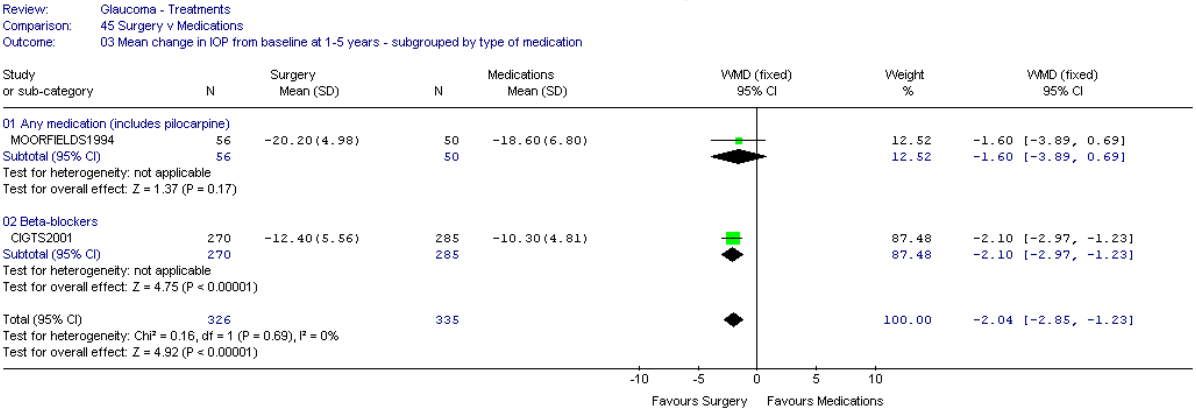


Figure 46 Trabeculectomy vs. pharmacological treatment – change in IOP from baseline at >5 yrs

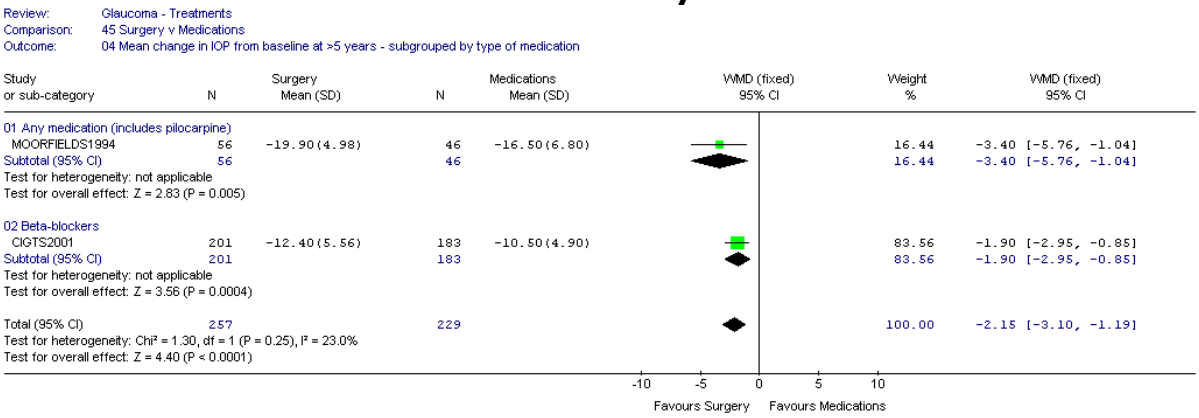


Figure 47 Trabeculectomy vs. pharmacological treatment – unacceptable IOP at 12 months

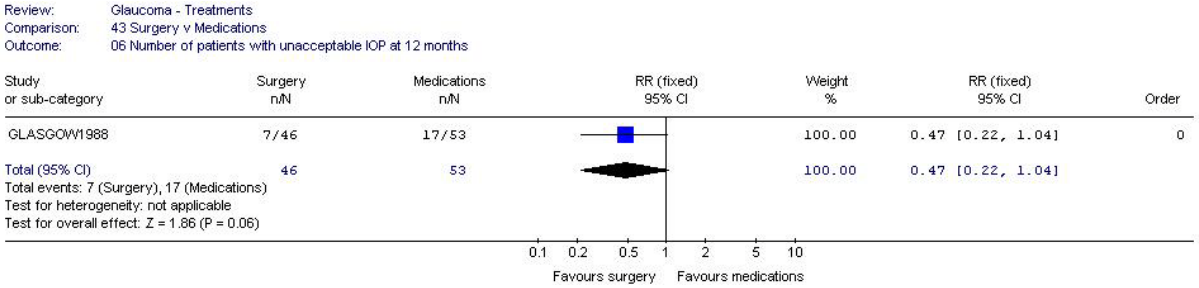


Figure 48 Trabeculectomy plus augmentation vs. trabeculectomy – unacceptable IOP

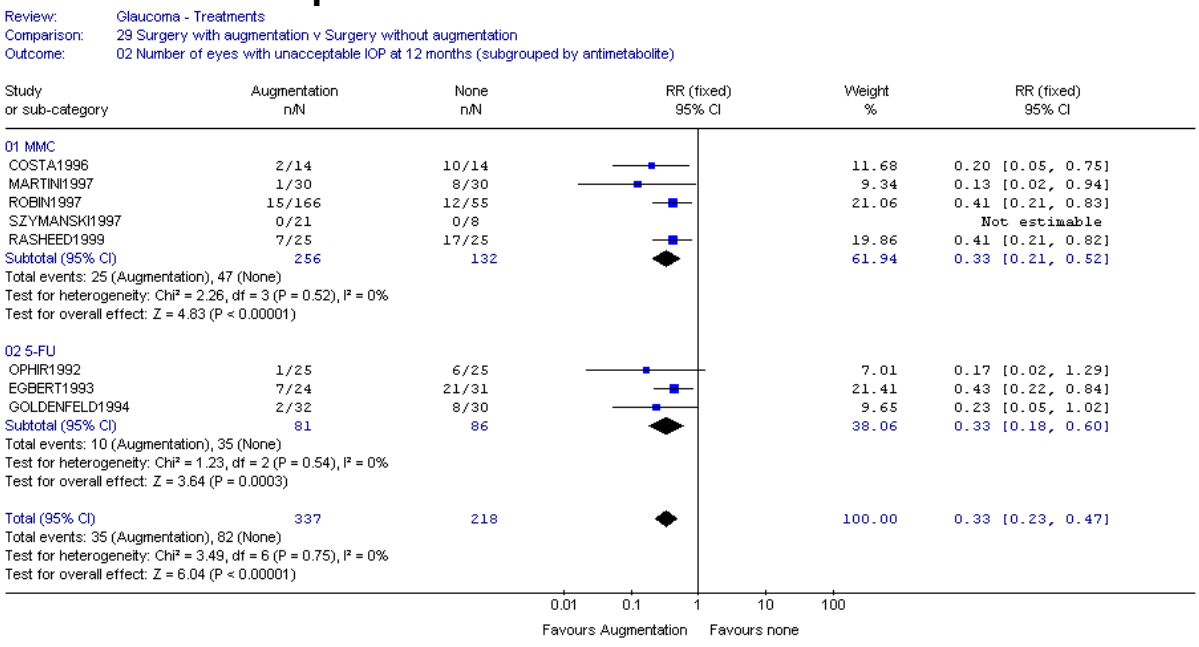


Figure 49 Trabeculectomy plus augmentation vs. trabeculectomy – complications: cataract formation

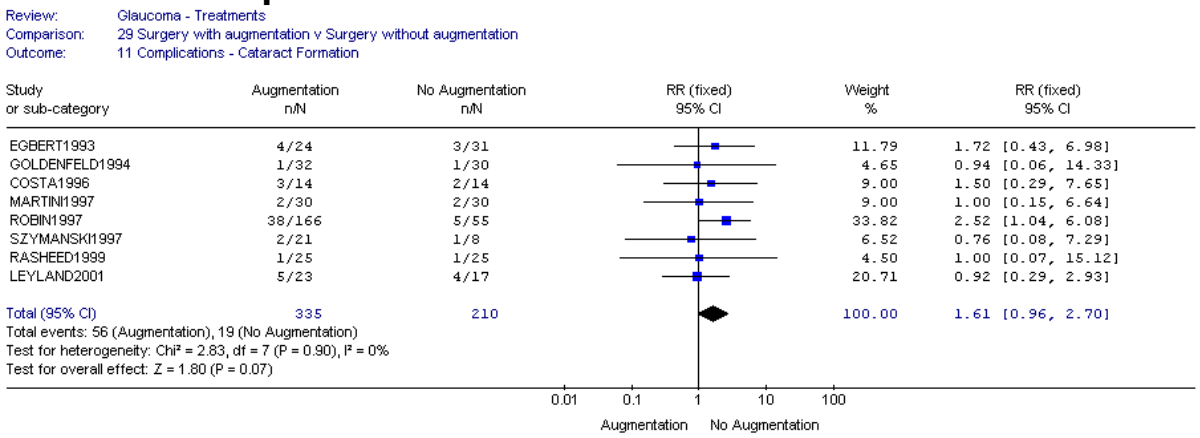


Figure 50 Trabeculectomy plus augmentation vs. trabeculectomy – complications: persistent hypotony

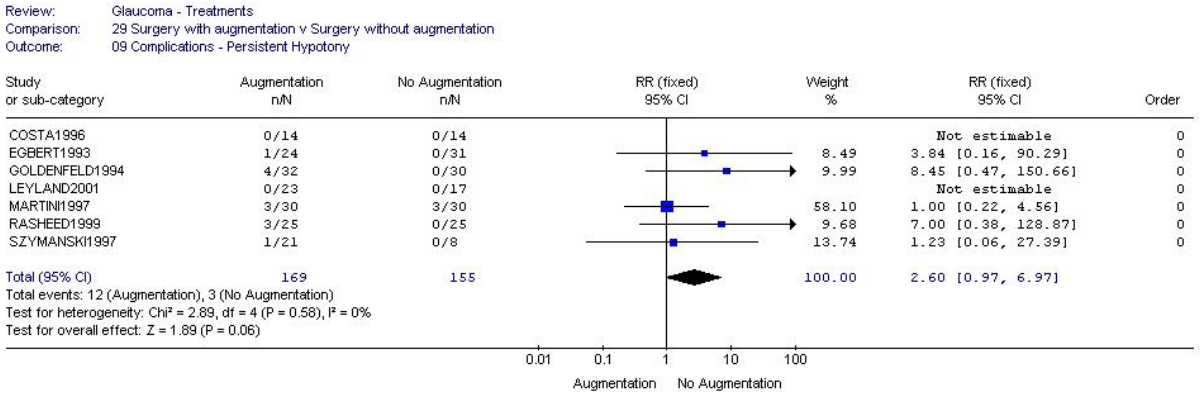


Figure 51 Trabeculectomy plus augmentation vs. trabeculectomy – complications: wound leaks

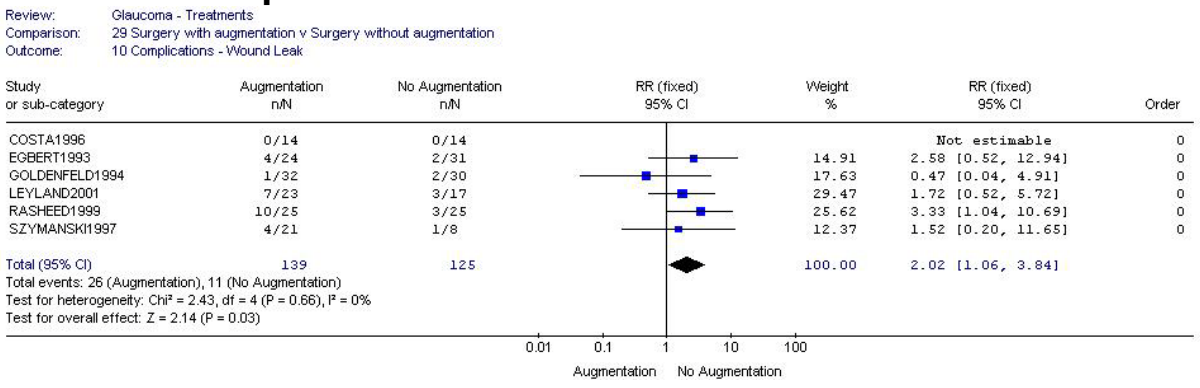


Figure 52 Trabeculectomy plus augmentation vs. trabeculectomy – complications: corneal epithelial defects

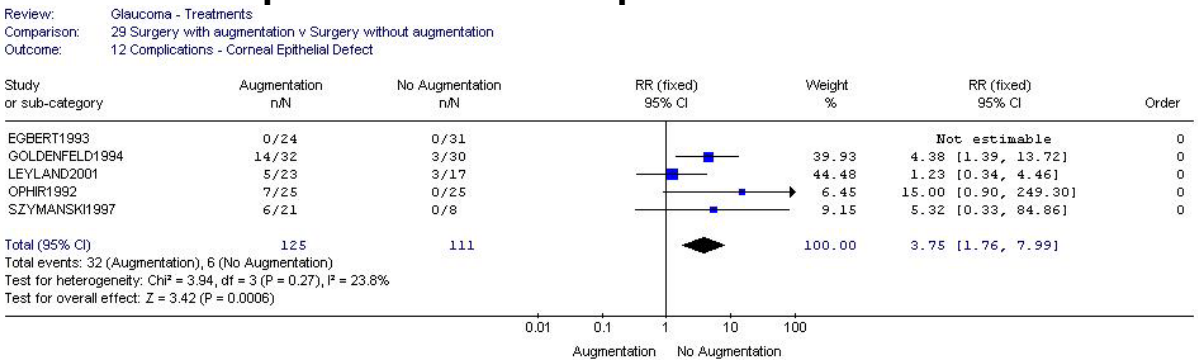


Figure 53 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – unacceptable IOP

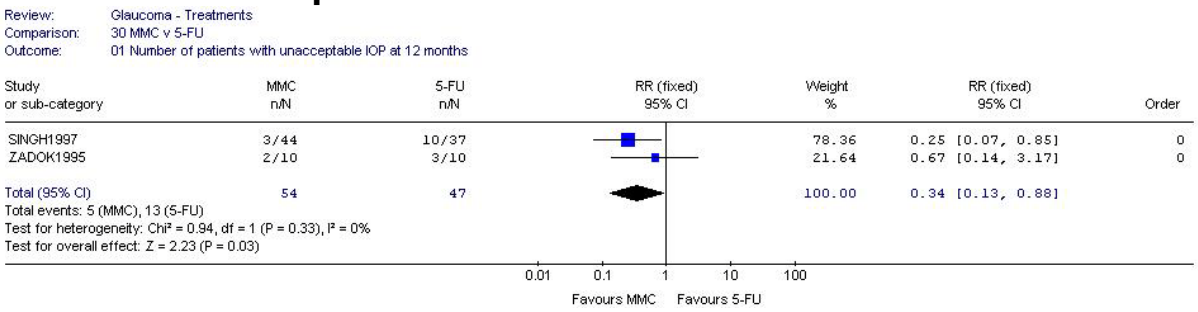


Figure 54 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: cataract formation

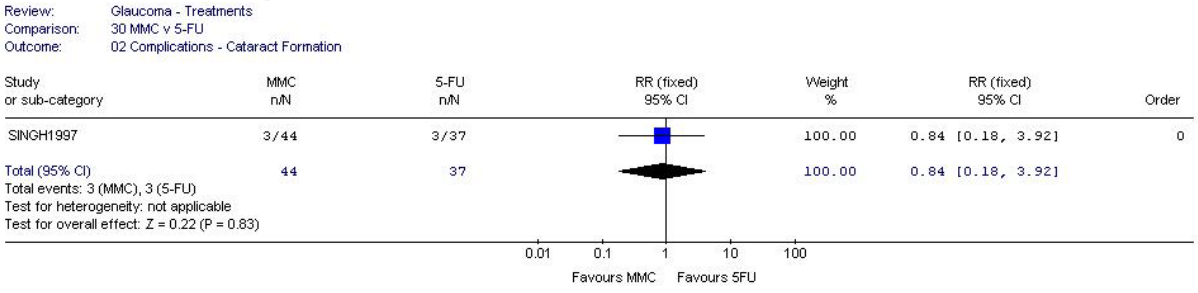


Figure 55 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: persistent hypotony

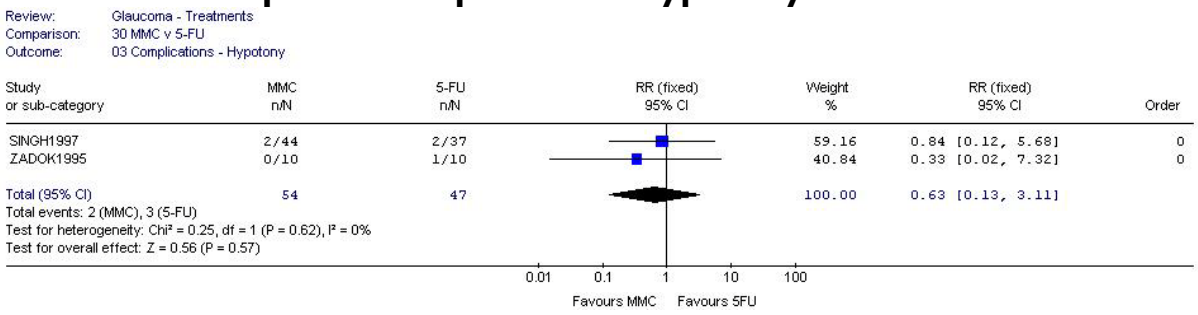


Figure 56 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: wound leaks

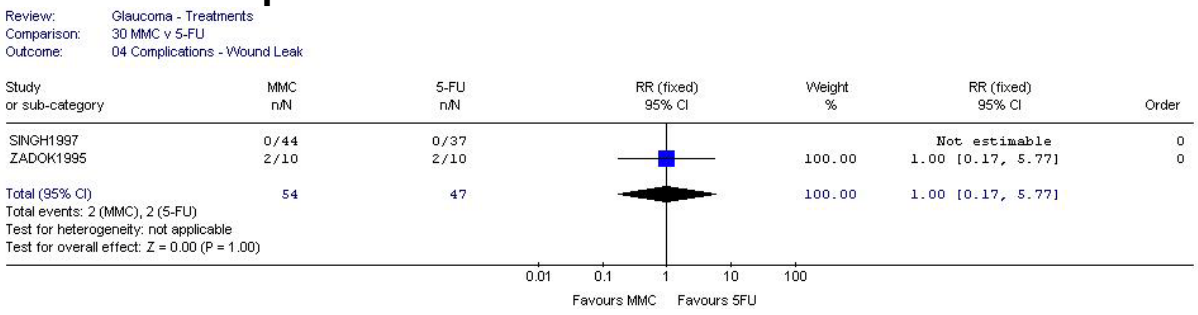


Figure 57 Trabeculectomy plus antimetabolite drug MMC vs. 5-FU – complications: corneal defects

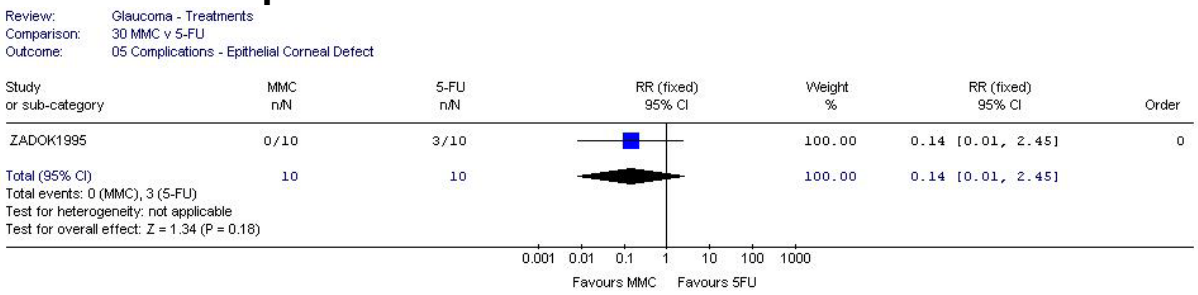


Figure 58 Viscocanalostomy vs. deep sclerectomy – change in IOP from baseline at 6 months

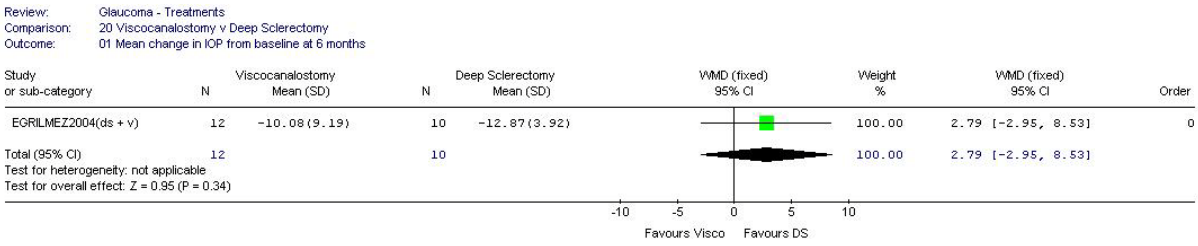


Figure 59 Non-penetrating surgery vs. trabeculectomy – change in IOP from baseline at 6 months

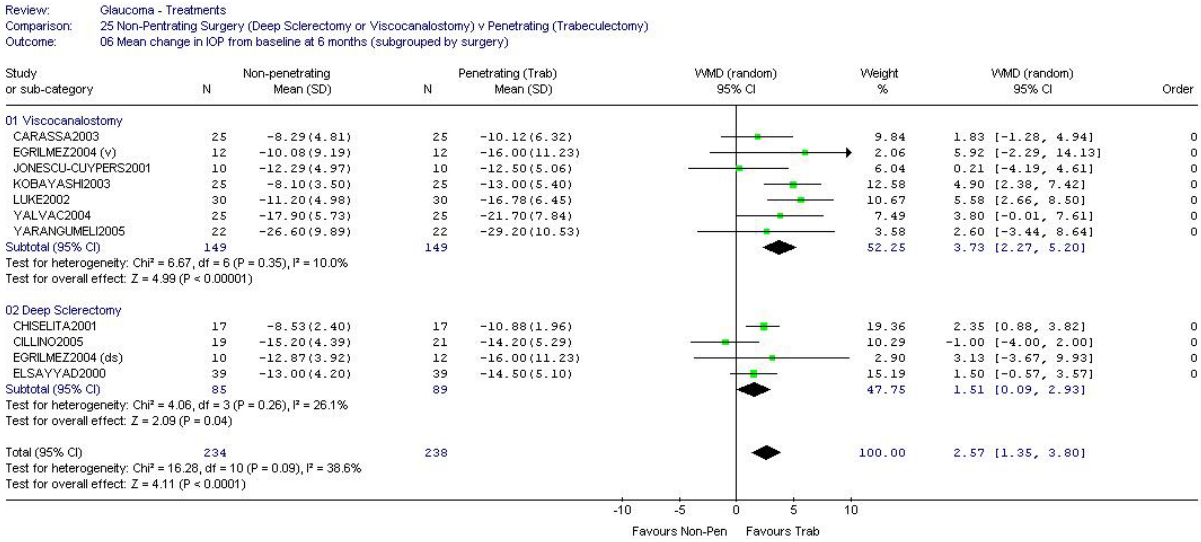


Figure 60 Non-penetrating surgery vs. trabeculectomy – change in IOP from baseline at 12 months

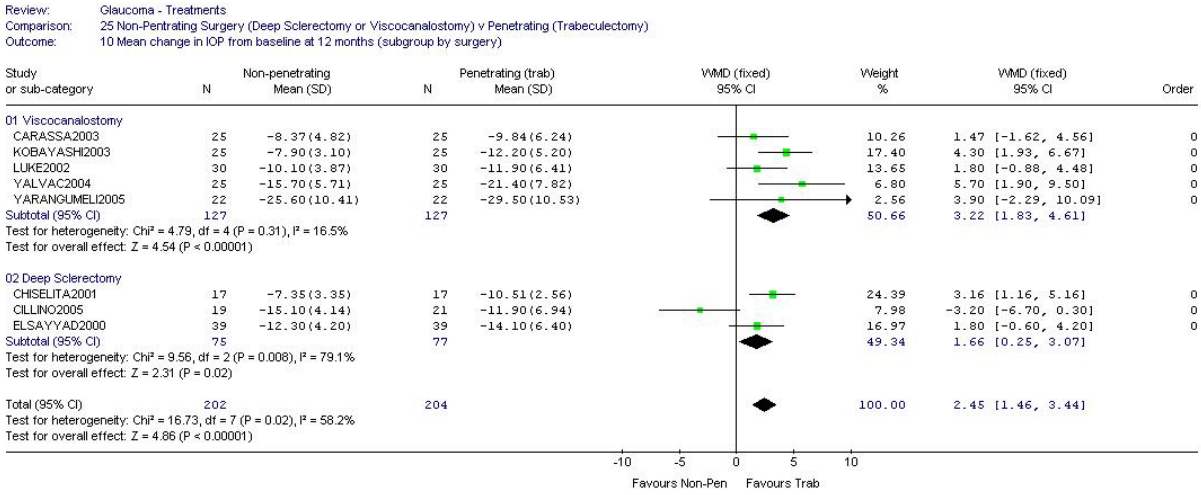


Figure 61 Non-penetrating surgery vs. trabeculectomy - unacceptable IOP

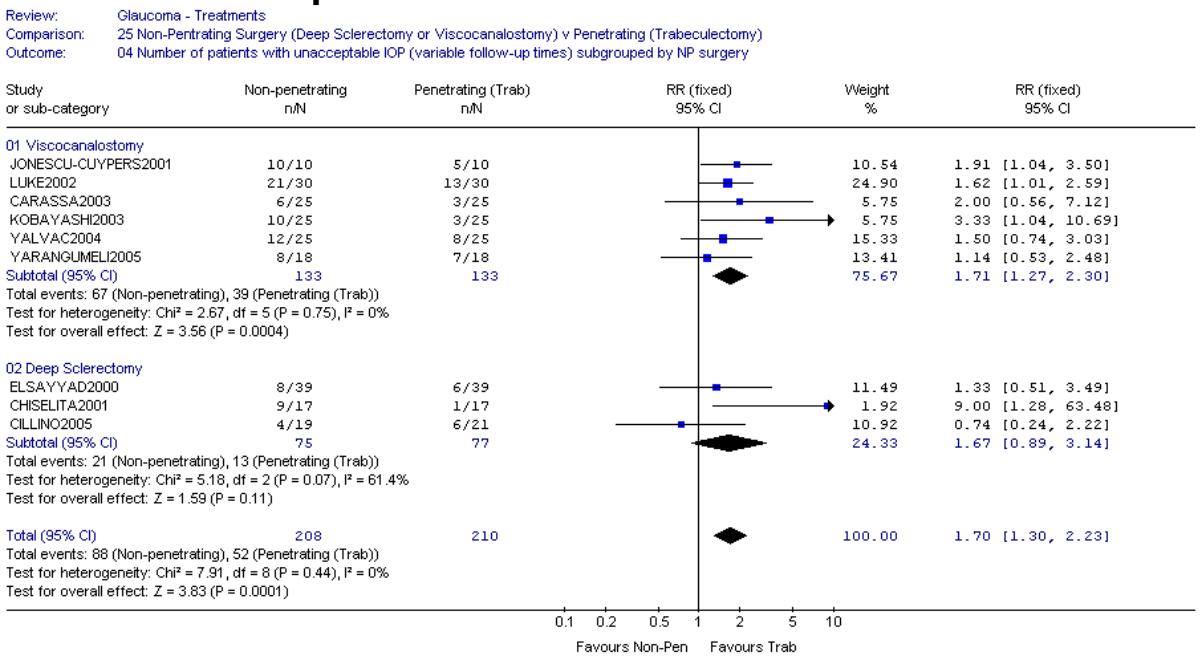


Figure 62 Non-penetrating surgery vs. trabeculectomy – complications: cataract formation

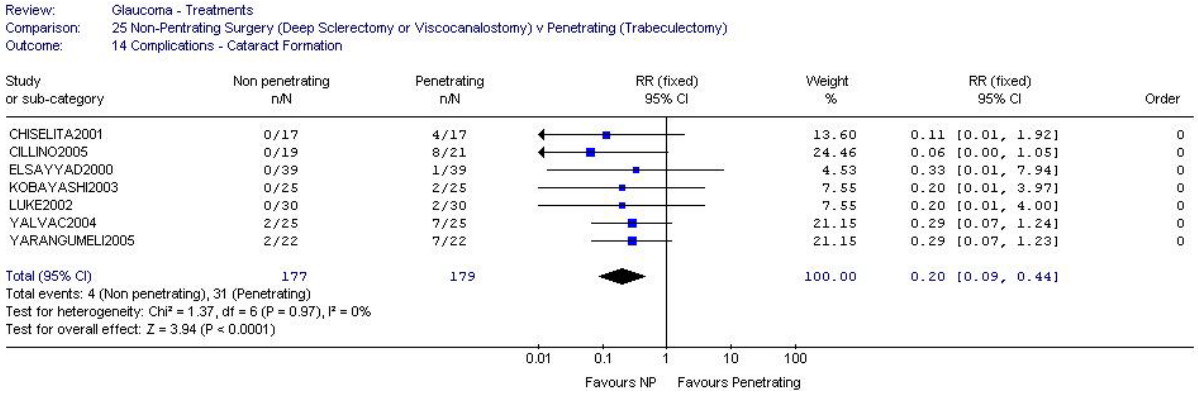


Figure 63 Non-penetrating surgery vs. trabeculectomy – complications: persistent hypotony

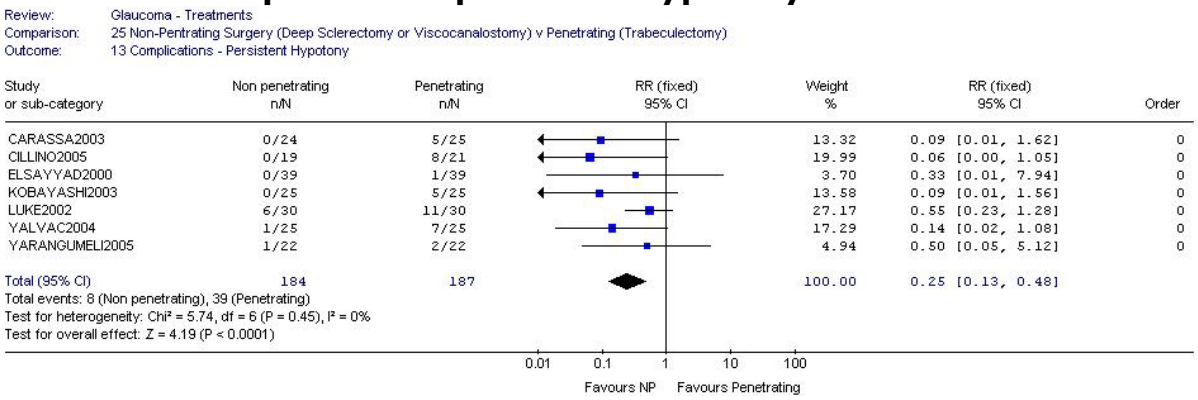


Figure 64 Non-penetrating surgery vs. trabeculectomy – complications: wound leaks

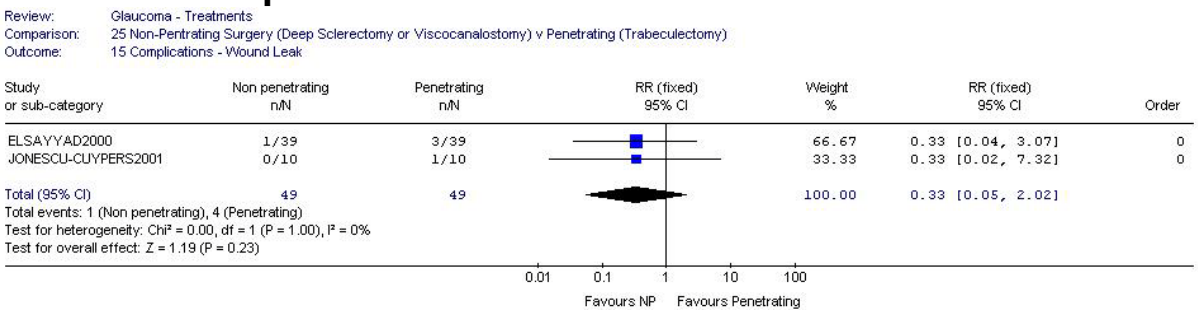
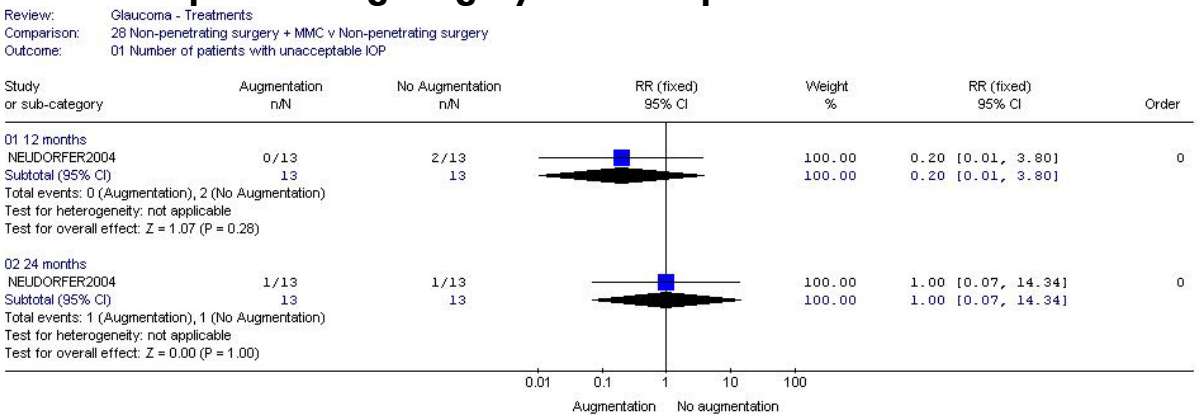


Figure 65 Non-penetrating surgery plus augmentation vs. non-penetrating surgery – unacceptable IOP



Appendix F

1 Cost-effectiveness analysis

1.1 Introduction

Most of the economic evidence of this guideline derives from original cost-effectiveness analyses carried out by the NCC-AC. The main cost-effectiveness analysis was carried out to answer the clinical questions on treatment of patients with OHT and COAG suspects (Chapter 7), and the clinical question on treatment of patients with COAG (Chapter 8). Throughout the guideline we refer to this analysis as 'NCC-AC model'.

A further cost analysis was carried out to answer the clinical questions on diagnosis and monitoring measurements (Chapters 4 and 5). Throughout the guideline we refer to this analysis as 'NCC-AC cost analysis'.

1.2 Methods

The GDG identified the initial treatment strategy for both COAG and OHT patients as a high priority area for economic analysis. Specifically, the aim was to determine the most cost-effective strategy for patients who have not been treated before. Therefore, the priority for economic evaluation was limited to the following interventions according to the availability of good data on their clinical effectiveness, current use and licensing as a first-choice treatment:

- no treatment
- medical treatment with prostaglandin analogues (PGA)
- medical treatment with beta-blockers (BB)
- trabeculectomy (for COAG patients only)

For this area a review of the literature was conducted followed by economic modelling of the cost-effectiveness of the listed interventions in England and Wales (1.3). The literature search and review methods can be found in 2.4 and 2.6.

The questions on clinical measurements at diagnosis and monitoring were assigned a medium priority for economic analysis and so only a simple cost-analysis (1.4) was performed.

1.3 NCC-AC model: Cost-effectiveness of treatment

Our aim in constructing the model was to determine the most cost-effective strategy in managing OHT and COAG patients from the point of diagnosis.

We found a number of economic evaluations in the published literature (Chapters 7 and 8) but still it was necessary to develop our own analysis to determine the most cost-effective treatment strategy for different subgroups of patients. We took this approach because we found limited applicability in the published economic evaluations, mainly because the important long-term consequences (i.e. development of blindness) were ignored[3], drugs were lumped together in a single medical treatment group[3,80,144], or important alternatives such as surgery were not considered[82]. Furthermore most of the published studies did not evaluate cost-effectiveness using the NICE reference case[3,82].

The medical interventions we compared in the model are those which are licensed to be used as first-line treatments (beta-blockers and prostaglandin analogues). For COAG patients, trabeculectomy was compared to beta-blockers and prostaglandin analogues.

The following general principles were adhered to:

- The GDG was consulted during the construction and interpretation of the model.
- When published data was not available we used expert opinion to populate the model.
- Model assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- We followed the methods of the NICE reference case[108]. Therefore costs were calculated from a health services perspective. Health gain was measured in terms of quality-adjusted life-years (QALYs) gained. Both future costs and QALYs were discounted at 3.5%.
- The model employed a cost-effectiveness threshold of £20,000 per QALY gained.

1.3.1 General method

Glaucoma is a progressive disease where a patient's sight can deteriorate and never recover. The model is thus represented by a Markov model where patients cannot go back to previous stages. The cycle length was set at 2 months as this was thought to be the minimum time after which a change in treatment could occur. All the probabilities, costs and health utilities were converted in order to reflect the two-month values.

When defining the COAG stages we have used an adapted version of the Hodapp, Parrish and Anderson classification (Table 168). We have opted for this staging system as it allows us to use costs and utility values associated with different severity levels of COAG already present in the literature (see 1.3.11 and 1.3.14).

It was also used in previous glaucoma economic models[14,80] and in the selected sources of probability of progression[14].

Compared to the original staging system, we have collapsed the last two stages (severe COAG and blindness) as there was an overlap of their definitions and a lack of data of progression in the absence of treatment from severe COAG to blindness.

Table 1 - Staging classification in the model

COAG STAGE	*MEAN DEFECT SCORE*
No COAG (a)	No visual field defect
Early	-0.01 to -6.00 dB
Moderate	-6.01 to -12.00 dB
Advanced	-12.01 to -20.00
Severe Visual Impairment	-20.01 or worse

(a) *Includes OHT patients*

Patients diagnosed with OHT could be initially treated with a beta-blocker or a prostaglandin analogue or could be offered no treatment until they develop COAG (Figure 66).

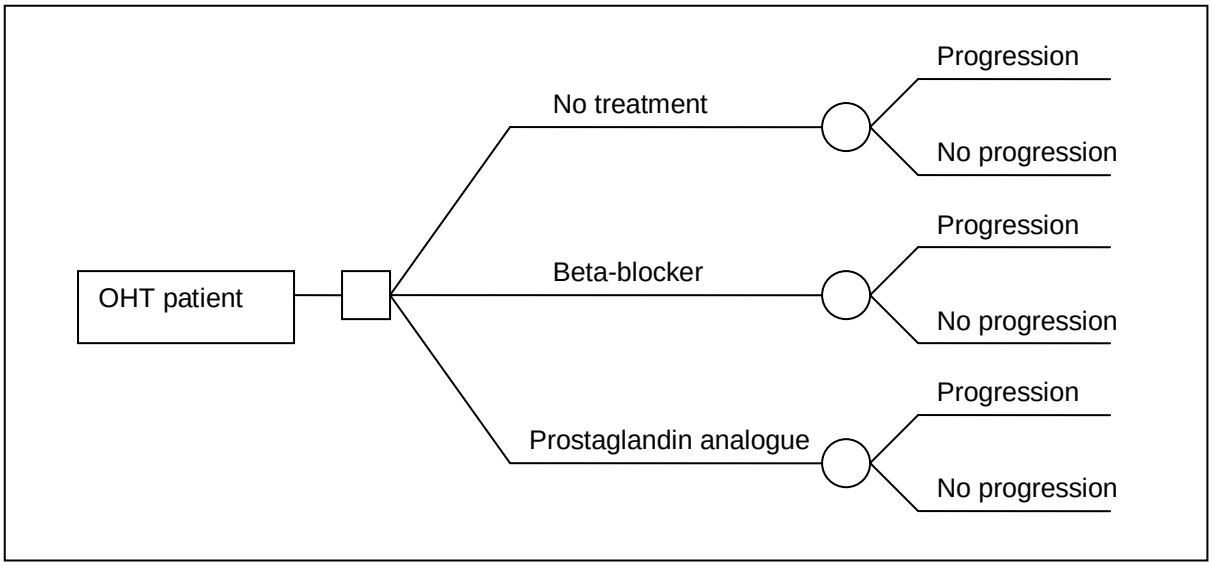


Figure 66 - Treatment strategies for OHT patients

Patients diagnosed with COAG could be treated either with a beta-blocker, a prostaglandin analogue, or trabeculectomy or could be offered no treatment until they progress to the following COAG stage (Figure 67). In the base case scenario patients were diagnosed with early COAG but in the sensitivity analysis we varied this assumption.

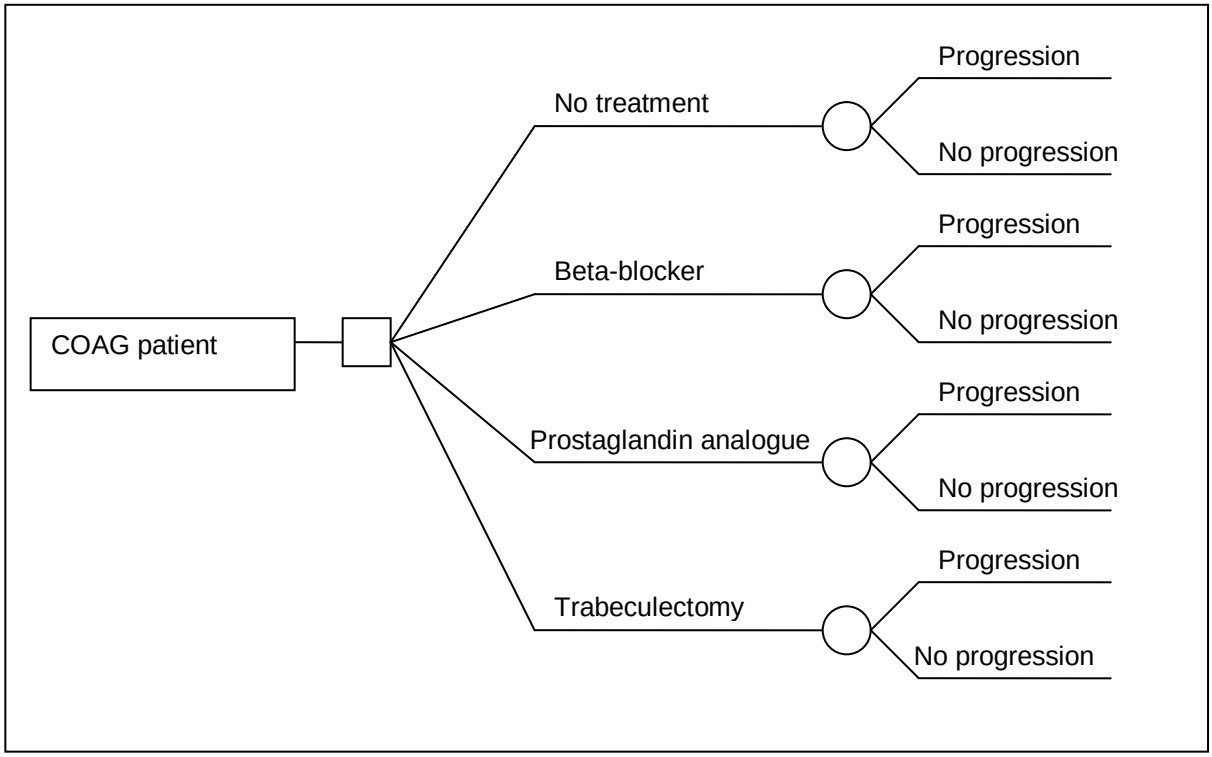


Figure 67 - Treatment strategies for COAG patients

The main effect of each strategy was considered to be the increase/decrease in risk of progression to the following COAG stages. However, in the literature the most commonly reported treatment outcome is the change in intraocular pressure (IOP). Two further systematic searches were conducted: one to find the Relative Risk (RR) of progression in OHT and in patients with COAG for each unit of IOP reduction (1.3.7), and the other one to find data on probability of progression from one stage to the next in both untreated and treated patients (1.3.5).

Each strategy is associated with upstream and downstream costs: the former are costs associated with the specific treatment while the latter are costs associated with the severity of the disease and thus dependent on the progression to later stages.

Some treatments could cause adverse events (see Chapters 7 and 8). Nevertheless not all of them result in important increased costs or reduced quality of life. We selected those more likely to occur and with a considerable impact on costs and quality of life using national sources[37] and expert opinion. Cataract and flat anterior chamber were the complications associated with trabeculectomy, while asthma was the only complication associated with beta-blockers for which incidence and annual cost per patient could be estimated. Other minor adverse events not requiring medical treatment are accounted for in the case of a change of COAG therapy.

For each strategy the expected healthcare costs and expected QALYs were calculated by estimating the costs and QALYs for each COAG stage and then multiplying them by the proportion of patients who would be in that stage as determined by the strategy taken.

We performed a probabilistic sensitivity analysis (PSA) to test the robustness of the results against the imprecision of these estimates and the other model parameters, and to obtain more accurate estimates of expected costs and QALYs.

In the base case of the OHT model, patients are 60 years old. However, from the review on risk of progression (see 1.3.5) we know that age is a significant risk factor for development of COAG. For this reason, we conducted a one-way sensitivity analysis on the age at decision point.

1.3.2 Time horizon

We considered the cost of treatment and health effects during a lifetime.

1.3.3 Key assumptions

In both COAG and OHT models the following assumptions were made:

a) In the absence of treatment, the change in IOP is equal to 0.

b) The change in IOP due to a treatment does not depend on whether the patient has COAG or OHT.

c) A patient starting with a prostaglandin analogue who demonstrates intolerance to this drug is switched to a beta-blocker.

d) A patient starting with a beta-blocker who demonstrates intolerance to this drug (including development of asthma) is switched to a prostaglandin analogue.

e) After a first switch in treatment, a second one can occur only after progression and thus its cost is included in the downstream cost of the stage.

f) When used after a treatment switch, beta-blockers and prostaglandin analogues have the same IOP lowering effect as when they are used as a first-choice treatment.

g) The severity of the condition is similar in both eyes of a patient.

In the COAG model the following assumptions were made:

a) In the base case the average age of patients at the beginning of the model is 72 years, as this was the mean age of COAG patients in the UK[154].

b) Patients are reviewed every three months.

c) The surgical procedure is trabeculectomy with or without enhancement.

d) Trabeculectomy is performed first in one eye then in the other after 2 months.

e) If post-surgery complications occur, the patient is treated appropriately and trabeculectomy is performed on the second eye if this has not already been done.

In the OHT model the following assumptions were made:

a) In the base case the average age of patients at the beginning of the model is 60 years, being the mid-point of the range 40-80 for which data on progression is available.

b) Untreated patients are reviewed on average every six months.

c) Treated patients are reviewed on average every three months.

1.3.4 Software

The cost-effectiveness analysis was conducted using TreeAge Pro 2007.

1.3.5 Baseline probability of progression

A search was conducted to identify papers looking at progression in OHT and COAG. We selected papers which reported the probability for one or more of the following progressions:

- from OHT to COAG in untreated patients
- from Early to Moderate COAG in treated and untreated patients
- from Moderate to Advanced COAG in treated and untreated patients
- from Advanced COAG to Severe Visual Impairment in treated and untreated patients

Only studies using a definite staging system and published after 1998 were included since it was GDG opinion that before that time the detection of COAG was not accurate. We found three studies in total matching our inclusion criteria:

Lee et al (2006)[85] is a retrospective cohort study where patients in OHT and COAG stages were followed up for 5 years to detect progression. It was excluded due to its small sample size (on average 25 patients in each stage) and short follow-up.

A cost-effectiveness study[80] reported the annual risk of developing COAG in untreated OHT patients based on the results of the Ocular Hypertension Treatment Study[50], a multicentre RCT with 1636 participants randomised to either treatment or no treatment and followed-up for a mean of 6 years. In addition to the estimate of probability of progression in the absence of treatment, the study[50] calculated the hazard ratio of each clinical parameter for developing COAG through a multivariate Cox proportional hazards model.

A Health Technology Assessment (HTA)[14] estimated the progression rates by COAG stage defined as mild, moderate and severe COAG, corresponding to our definitions of early, moderate and advanced COAG. The approach adopted was to use RCTs of treatment compared to control to calculate the progression rate by visual field mean defect. Since no RCT was found for the severe stage, its progression was projected from the previous stages.

Table 169 summarises the studies selected and their results.

Table 2 – Baseline probability of progressions

	Annual Probability Of Progression In Treated Patients	Annual Probability Of Progression In Untreated Patients	Source
OHT to COAG	-	2.2% (a)	Ocular Hypertension Treatment Study[50,80]
Early to Moderate COAG	20%	25%	HTA – Burr (2007)[14]
Moderate to Advanced COAG	7%	11%	HTA – Burr (2007)[14]
Advanced COAG to Severe Visual Impairment	6%	10%	HTA – Burr (2007)[14]

(a) Average value. See Table 170 and Table 171 for all the combinations of risk factors.

The calculation of the probability of conversion from OHT to COAG was based on different combinations of those parameters that resulted in significant risk factors for the progression from OHT to COAG. Following the exclusion of pattern standard deviation and cup-disc ratio since they are already clinical signs of COAG, the significant risk factors identified were age, IOP and central corneal thickness (CCT). First we inputted the probability of progression for each age group in the model (Table 170), and then we multiplied this by the RR resulting from the combination of IOP and CCT (Table 171) as follows:

- pCOAG = pCOAG[age] x RR

Table 3 - Probability of developing COAG in OHT patients (a)

Age group	Annual probability of progression in untreated patients
40-49 years	1.50%
50-59 years	1.90%
60-69 years	2.27%
70-80 years	2.69%

(a) Source: Kymes et al (2006)[80]

Table 4 - Relative risk for progression to COAG in OHT patients (a)

IOP	CCT	RR
>21 – 25 mmHg	>590 µm	0.16
>25 – 32 mmHg	>590 µm	0.49
>21 – 25 mmHg	555-590 µm	0.73
>25 – 32 mmHg	555-590 µm	1.06
>21 – 25 mmHg	≤555 µm	1.39
>25 – 32 mmHg	≤555 µm	2.93

(a) *Source: Gordon et al (2002)[50]*

The original IOP categories reported in the study[50] were IOP >21- 23.75 mmHg, IOP 23.75-25.75 mmHg, and IOP 25.75 - 32 mmHg. The GDG felt that keeping the middle group was clinically meaningless as the range limits are so close; therefore we incorporated this group into the two remaining groups IOP >21 – 25 mmHg and IOP >25 – 32 mmHg. The CCT categories in the study were CCT>588µm, CCT 555-588 µm, and CCT≤555 µm, which for clinical simplicity were rounded to CCT>590 µm, CCT 555-590 µm, and CCT ≤555 µm.

1.3.6 IOP reduction

Data on change in IOP from baseline due to each treatment was derived from the systematic review of clinical effectiveness of treatments in OHT and COAG patients (Chapter 7 and 8). No studies comparing prostaglandin analogues to no treatment and trabeculectomy to no treatment met the inclusion criteria. The data used in the model is summarised in Table 172 and correspond to the results of the forest plots in Figure 5, Figure 10, and Figure 44 in Appendix E. Among the comparisons of trabeculectomy with any medical treatment, the Collaborative Initial Glaucoma Treatment Study (2001)[89] was the only study comparing beta-blockers to trabeculectomy and thus the only trial included for this specific comparison (Figure 44 – subgroup 2).

Table 5 – Mean difference in change in IOP from baseline

	Mean difference
Beta-blockers vs No treatment	- 2.88 mmHg
Prostaglandin analogues vs Beta-blockers	- 1.32 mmHg
Trabeculectomy vs Beta-blockers	- 3.6 mmHg

1.3.7 IOP reduction and progression

We conducted a search in order to find a measure of the link between IOP reduction and protection against progression. Two scenarios were considered:

- a link between IOP reduction and reduced conversion from OHT to COAG,
- a link between IOP reduction and reduced progression of established COAG.

We included only studies reporting the RR of each mmHg reduction in IOP for progression or conversion, defined by deterioration in visual field or optic nerve appearance or both.

We found a study reporting the RR of developing COAG from OHT per unit of IOP reduction[50] and two studies reporting the RR of progression in COAG patients per unit of IOP reduction[86,87]. Leske et al (2007)[87], an update of Leske et al (2003)[86], is more up to date, and more conservative and so we used this in the base-case model.

In OHT patients, the percentage reduction in the probability of developing COAG was 10% per mmHg of IOP reduction. In COAG patients, the percentage reduction in the probability of progressing was 8% per mmHg of IOP reduction.

The overall effectiveness of each intervention was calculated by multiplying the mean difference in IOP reduction with the percentage reduction in progression per mmHg of IOP reduction.

Table 6 – Overall Effectiveness of interventions

INTERVENTION	MEAN CHANGE IN IOP (mmHg)	PROGRESSION REDUCTION per mmHg change in IOP		PROGRESSION REDUCTION (overall effectiveness) Mean change in IOP * Progression Reduction/mmHg for each treatment option	
		OHT	COAG	OHT	COAG
No treatment	0	10%	8%	0	0
Beta-blockers	2.88	10%	8%	29%	23%
Prostaglandin analogues	4.2	10%	8%	42%	34%
Trabeculectomy	6.48	NA	8%	NA	52%

1.3.8 Probability of progression after treatment

In each branch of the model where patients received a treatment, the baseline probability of progression in the absence of treatment was adjusted by the overall effectiveness of the respective treatment:

- Baseline probability * (1-overall effectiveness)

For example, a patient with Early COAG would have an annual probability of progression to Moderate COAG of 25% if untreated, and 25%*(100%-34%) = 16.5% if treated with a prostaglandin analogue.

The probability thus calculated was used for the time during which the patients received that treatment in the model. Once a switch in treatment occurred without progression this probability was recalculated according to the new drug used. Once a patient has progressed to the following stage, the new probability is the baseline probability in treated patients for that stage (Table 169). The rationale is that after progression any new treatment could be introduced, for which we cannot estimate the effectiveness. As a consequence, we used progression estimates for nonspecific treatments.

1.3.9 Other probabilities

Other probabilities used in the model were:

- Probability of developing asthma after use of beta-blockers: it was estimated from a prospective cohort study[74] comparing the difference in respiratory disease in 2,645 patients treated with beta-blockers to 9,094 unexposed patients. The difference between the proportions of patients given a new prescription of drug for reversible airways obstruction in 12 months after treatment was 3.3%. The same study[74] reports that the risk of respiratory problems ceases to be significant after the first year of exposure; therefore the probability of developing asthma is kept in the model only within the first year.

- Probability of discontinuation due to reasons other than treatment failure: we found one UK study[166] reporting the proportion of patients discontinuing treatment for reasons other than treatment failure (i.e. adverse events, intolerance). In this study, 19 out of 149 patients (13%) treated with prostaglandin analogues and 158 out of 632 patients (25%) treated with beta-blockers discontinued within 1 year. From the latter figure we subtracted 3.3% which was the proportion of patients developing asthma that would have been included in the discontinuation of beta-blockers; the remaining annual probability for this group is 21.7%. Data for later years were not available; thus these probabilities were used only during the first year of treatment.

- Probability of post-surgery complications: the GDG identified those complications that require further treatment and are therefore associated with extra costs. Rare (with an incidence of1% or less) and promptly resolving complications were excluded. Cataract and flat anterior chamber were the two complications identified. There was overall agreement between experts' estimates and national sources on the incidence of cataract. The probability was obtained from the National Survey of Trabeculectomy[37] considering only the cases that required cataract extraction (2.5%). The incidence of flat anterior chamber requiring treatment was estimated by experts as 0.75%, reported in the National Survey[37] as 0.2%, and in the Moorfields Glaucoma service annual audits 2001-2007 as 4%. We decided to use an average of these figures (1.65%) to estimate the probability of reformation of anterior chamber. Cataract extraction and reformation of anterior chamber were assumed to occur in the model only in the two months (1cycle) following surgery for both the first eye and the second eye operation.

- Probability of needing medication after surgery: the probability of adding a medication because of poor IOP control after trabeculectomy was obtained from the National Survey of Trabeculectomy[38]. Patients requiring post-operative anti-glaucoma medications were 147/1105 (13.3%) after 1 year. This probability was also used in the following years.

1.3.10 Life expectancy

Life expectancy in patients with COAG or OHT was assumed to be the same as the general population in England and Wales. Life expectancy was estimated for each age by calculating the mean of the figures for men and women reported in the Life Tables for the general population of England and Wales in the year 2004-2006 in the Government Actuary Department (http://www.gad.gov.uk/Demography_Data/Life_Tables/Interim_life_tables.asp)

1.3.11 Quality of life

The utility scores in Table 174 are a measure of the quality of life associated with each of the COAG stage on a scale from 0 (death) to 1 (perfect health). A systematic search for quality of life in OHT and COAG patients was performed. Studies were included if health state utility values were reported or obtainable for stages separately and they were based on visual field defect.

One study[119], using data obtained from Brown et al (2003)[12], was selected that applied utilities for visual acuity to each category of visual field loss. Two functions to calculate health utilities for each continuous dB increment of visual field defect were developed. In order not to favour the most effective treatment, we adopted the formula that resulted in the most conservative estimate of quality of life detriment resulting from visual field defects:

III $\text{Health utility} = 0.98991 + 0.0022 * dBs - 0.00080518 * dBs^2$

where dBs are expressed as an absolute numbers and is therefore a positive number.

Since the stages in the model were defined as ranges of visual field defect (Table 168), it was possible to calculate the upper and lower limits and the central utility score for each stage by substituting the range limits and the central value of the stage definition. The central value of the severe visual impairment stage was assumed to be -26dB following the World Health Organization definition of blindness as reported in Rein et al (2007)[119], while the upper limit was assumed to be -30dB. The quality of life in OHT patients was assumed to be equal to perfect health as there was no visual field defect.

Table 7 - Health Utilities by COAG stage

STAGE	LOWER LIMIT	UPPER LIMIT	CENTRAL VALUE
OHT	-	-	1
Early COAG	0.974	0.990	0.989
Moderate COAG	0.900	0.974	0.944
Advanced COAG	0.712	0.900	0.819
Severe Visual Impairment	0.331	0.712	0.503

When we compared our estimates with other published studies[16,53,78,84] we found that overall we had been more conservative.

Adverse events were assumed to be negligible in terms of quality of life because they could be promptly treated, with the exception of asthma. A search for quality of life measures in the CEA Registry (https://research.tufts-nemc.org/cear/default.aspx) retrieved a study[130] where the health utility in treated asthma patients was 0.84. Hence it was assumed that treated asthma symptoms produce a decrease in quality of life of 0.16 over one year. This is probably an overestimation because the treatment with beta-blockers should be immediately discontinued with the consequent reduction of symptoms. On the other hand, beta-blockers are known to have other important adverse events for which incidence, costs and quality of life detriment could not be estimated.

1.3.12 Calculating QALYs gained

For each strategy, the expected QALYs per cohort of patients in each cycle are calculated as follows:

IV Expected QALYs = $U_{OHT} \times P_{OHT} + U_e \times P_e + U_m \times P_m + U_a \times P_a + U_b \times P_b + P_{ast} \times U_{ast}$ where

U_{OHT} , U_e , U_m , U_a , U_b = the utility score for each stage

U_{ast} = the utility detriment due to asthma (negative number)

P_{OHT} , P_e , P_m , P_a , P_b = the proportion of patients in each of the COAG stage at the end of each cycle

P_{ast} = the proportion of patients developing asthma in each cycle

The proportion of patients in each COAG stage depends on the progression reduction of the treatment and on the proportion of patients still alive according to the mortality rate for the general population of England and Wales.

The overall lifetime expected QALYs are given by the sum of QALYs calculated for each cycle. The incremental QALYs gained associated with a treatment strategy are calculated as the difference between the expected QALYs with that strategy and the expected QALYs with the comparator.

1.3.13 Upstream treatment costs

Upstream treatment costs are those directly associated with the treatment strategy considered and so those arising before a progression. The resources used in each cycle for the different strategies are summarised in Table 175. These resources are used only until the patient remains in the treatment strategy assigned at the beginning of the model. Patients in the beta-blocker and prostaglandin analogue arms can interchange treatment in which case the cost of an additional visit is added and the cycle cost is calculated according to the new treatment.

Table 8 - Resources used

	No Treatment	Beta-blockers	Prostaglandin analogues	Surgery	Source
Drugs	-	2 bottles of Timolol	2 bottles of either Latanprost, Travoprost, Bimatoprost	Used post-operatively: 1 bottle Chloramphenicol + 4 bottles Predforte + 1bottle Cyclopentolate 1bottle of either a prostaglandin or a beta-blocker in the two months between surgery in first eye and second eye	Expert opinion
Trabeculectomy inpatient	-	-	-	34% in both first and second cycle (first and second eye)	Hospital Episode Statistics for 2006/07
Trabeculectomy daycase	-	-	-	66% in both first and second cycle (first and second eye)	Hospital Episode Statistics for 2006/07
Monitoring visits - OHT	0.33 (a)	0.33 (a) + 1 if treatment switch	0.33 (a) + 1 if treatment switch	0.33 (a)	Expert opinion and recommendation in the Guideline
Monitoring visits - COAG	0.67 (b)	0.67 b + 1 if treatment switch	0.67 b + 1 if treatment switch	0.67 (b)	Expert opinion and recommendation in the Guideline

(a) .One visit every 6 months
(b) One visit every 3 months

The costs of the resources used are reported in Table 176. All the cost figures are expressed in 2006 Pound Sterling.

Table 9 - Cost per unit of resource used

	COST	SOURCE
Bottle of beta-blocker	£3.12	BNF 56
Bottle of prostaglandin analogue	£11.70 (a)	BNF 56
Post-operative drug treatment	£9.7 (b)	BNF 56
Trabeculectomy – inpatient	£1,316	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined (HRG code BZ18Z)
Trabeculectomy – daycase	£789	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined (HRG code BZ18Z)
Trabeculectomy – weighted average cost	£968 (c)	NCC-AC calculation
Cost of monitoring visit	£62	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined – Consultant led follow up attendance outpatient face to face - specialty code 130 Ophthalmology

(a) Mean cost of Travoprost, Latanoprost and Bimatoprost
(b) Cost of 1 Chloramphenicol + 4 Predforte + 1Cyclopentolate (£2.72 + 4 x £1.50 + £0.97)
(c) Proportion of inpatient x cost inpatient + proportion daycase x cost daycase

1.3.14 Downstream treatment costs

While a calculation of the resources used was made for the upstream costs, it would have been inaccurate if not impossible to do that for the costs arising after a disease progression. We conducted a systematic search on the cost of glaucoma stages and we selected a cost-of-illness study[151] reporting the direct healthcare cost per patient associated with each COAG stage. We chose this study because the staging system was the same that we adopted (Hodapp, Parrish and Anderson classification, 1.2), and it contained UK data. The figures in Table 177 were obtained by converting the 2004 Euros into GBP by a conversion factor of 0.67, which was the reciprocal of the one used by the author to convert GBP into Euros.

Table 10 – Annual cost of COAG stage per patient

Stage	Cost year per patient (£)	Source
Early COAG	399	Traverso et al (2006)[151]
Moderate COAG	449	Traverso et al (2006)[151]
Advanced COAG	357	Traverso et al (2006)[151]

In the paper, the costs of severe COAGand blindness did not account for social costs, thus leading to an underestimation of the true costs. Therefore for the last stage (Severe Visual Impairment) we based our cost analysis on the services

provided to patients with blindness as described in Meads and Hyde (2003)[96]. Table 178 illustrates the services considered in our analysis, the calculation of their costs, and the proportion of patients receving each service as reported in Meads and Hyde (2003)[96]. The same study includes the cost of depression and hip replacement in individuals with visual impairment. We did not use these data as they were not controlled for incidence in the general population.

Table 11 - Cost of severe visual impairment

Service	Cost (£)	Source	Proportion of patients receiving the service
Blind registration	122.78 (one-off)	Pay Circular 3/2008 – Annex A Section 5 http://www.nhsemployers.org/pay-conditions/pay-conditions-2339.cfm%20Pay%20circular%20M&D%20(3/2008)	95%
Low vision aids	150 (one-off)	Meads and Hyde (2003)[96] – figures uplifted to year 2008	33%
Low vision rehabilitation	207 (one-off)	Curtis (2007)[28] - NHS community occupational therapist cost of episode of care including qualification	11%
Community care	8,216	Curtis (2007)[28] - Annual cost for a local authority home care worker	6%
Residential care	16,344	Curtis (2007)[28] - Annual cost of private residential care assuming that 30% of residents pay themselves	30%

The cost of OHT was not used in the model because it is always dependent on the treatment strategy adopted (upstream cost).

For each strategy, the expected cost per cohort of patients in each cycle is calculated as follows:

$$\text{Expected cost} = UC_a \times P_a + \Sigma\, DC_i \times P_i$$

where

UC_a = upstream cost of the initial treatment strategy

P_a = proportion of patients in the initial treatment strategy

DC_i = downstream cost of stage i

P_i = proportion of patients in the stage i

and where stage i could be any later stage

The proportion of patients in each COAG stage depends on the magnitude of the progression reduction of the treatment and on the proportion of patients still alive according to the mortality rate for the general population of England and Wales.

The overall lifetime expected costs are given by the sum of costs calculated for each cycle. The incremental cost associated with a treatment strategy is calculated as the difference between the expected cost with that strategy and the expected cost with the comparator.

1.3.15 Adverse events and complications costs

Three main adverse events and complications were identified (1.3.9) and their costs estimated as shown in Table 179.

We searched for UK cost of illness studies on asthma. We found one study [160] but being too old we opted for a bottom-up approach. We estimated the cost of an annual treatment with beta-agonist and corticosteroids from a NICE Technology Appraisal[11].

The cost of treating the two post-operative complications, cataract and anterior flat chamber, corresponds to the cost of cataract extraction and anterior chamber reformation.

Table 12 - Cost of adverse events and complications

	COST	SOURCE
Annual cost of asthma treatment	£147 (a)	Brocklebank et al (2001)[11]
Cataract extraction	£977 (b)	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined – HRG code BZ03Z
Reformation of anterior chamber of eye	£974 (c)	National Schedule of Reference Costs 2006-07 for NHS Trust & PCT Combined – HRG code BZ19Z

(a) annual cost of beta-agonist + corticosteroids = 105+42 = £147
(b) all daycase
(c) weighted cost - £556 x 46%(daycase) + £1,330 x 54%(inpatient)

In addition, a treatment change following asthma is always associated with the one-off cost of an extra visit (£62).

1.3.16 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed to assess the robustness of the OHT and COAG models results to plausible variations in the model parameters.

Probability distributions were assigned to each model parameter, where there was some measure of parameter variability (Table 180). We then re-calculated the main results 10000 times, and each time all the model parameters were set simultaneously, selecting from the respective parameter distribution at random. When some distributions were used in either the OHT model or in the COAG model only, this is specified in Table 180.

Table 13 - Parameters used in the probabilistic sensitivity analysis (α)

Description of variable	Mean value	Probability distribution	Parameters	Source	Model
Mean difference in change in IOP from baseline – BB vs No Treatment	- 2.88 mmHg	Normal	SD = 0.643	Systematic review of clinical effectiveness	COAG and OHT models
Mean difference in change in IOP from baseline – PGA vs BB	-1.32 mmHg	Normal	SD = 0.24	Systematic review of clinical effectiveness	COAG and OHT models
Mean difference in change in IOP from baseline – trabeculectomy vs BB	-3.6 mmHg	Normal	SD = 0.418	Systematic review of clinical effectiveness	COAG model
Age at diagnosis of OHT	60 years	none		assumption	OHT model
Age at diagnosis of COAG	72 years	Custom distribution	age range/probability: 40-44 1.6% 45-49 2.3% 50-54 3.5% 55-59 5.4% 60-64 8.8% 65-69 13.4% 70-74 16.3% 75-79 18.5% 80-84 16.3% 85-89 13.9%	Tuck et al (1998)[154]	COAG model
Cost of Early COAG	£399	Gamma	α = 61.46 λ = 0.154 based on +/-25% for upper and lower bounds	Traverso et al (2006)[151]	OHT model
Cost of Moderate COAG	£449	Gamma	α = 61.46 λ = 0.137 based on +/-25% for upper and lower bounds	Traverso et al (2006)[151]	COAG and OHT models
Cost of Advanced COAG	£357	Gamma	α = 61.46 λ = 0.172 based on +/-25% for upper and lower bounds	Traverso et al (2006)[151]	COAG and OHT models
Cost of Severe Visual Impairment	see 1.3.14	none		NCC-AC calculation of cost of Severe Visual Impairment	COAG and OHT models

Cost of Blindness Registration	£122.78	Gamma	α = 61.46 λ = 0.500 based on +/-25% for upper and lower bounds	Pay Circular 3/2008 – Annex A Section 5 http://www.nhsemployers.org/pay-conditions/pay-conditions-2339.cfm%20Pay%20circular%20M&D%20(3/2008)	COAG and OHT models
Cost of low-vision aids	£150	Gamma	α = 61.46 λ = 0.410 based on +/-25% for upper and lower bounds	Meads and Hyde (2003)[96]	COAG and OHT models
Cost of low-vision rehabilitation	£207	Gamma	α = 61.46 λ = 0.297 based on +/-25% for upper and lower bounds	Curtis (2007)[28]	COAG and OHT models
Cost of community care for blindness	8,216	Gamma	α = 61.46 λ = 0.007 based on +/-25% for upper and lower bounds	Curtis (2007)[28]	COAG and OHT models
Cost of residential care for blindness	16,344	Gamma	α = 61.46 λ = 0.004 based on +/-25% for upper and lower bounds	Curtis (2007)[28]	COAG and OHT models
Cost of beta-blockers	see Table 176	none		BNF 56	COAG and OHT models
Cost of prostaglandin analogues	see Table 176	none		BNF 56	COAG and OHT models
Cost of trabeculectomy	see 1.3.13	none		National Schedule of Reference Costs 2006-07 – Glaucoma category 2 (HRG BZ18Z)	COAG model
Cost of trabeculectomy – inpatient	£1,316	Gamma	α = 7.55 λ = 0.0057 based on IQR	National Schedule of Reference Costs 2006-07	COAG model

Cost of trabeculectomy – daycase	£789	Gamma	α = 12.03 λ = 0.015 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Cost of follow-up visit	£62	Gamma	α = 14.45 λ = 0.233 based on IQR	National Schedule of Reference Costs 2006-07	COAG and OHT models
Cost of asthma	£147	Gamma	α = 61.46 λ = 0.42 based on +/-25% for upper and lower bounds	Broklebank et al (2001)[11]	COAG and OHT models
Cost cataract extraction	£977	Gamma	α = 11.77 λ = 0.014 based on IQR	National Schedule of Reference Costs 2006-07 non-phacoemulsification cataract surgery (HRG code BZ03Z)	COAG model
Cost anterior chamber reformation	See 1.3.15	none		National Schedule of Reference Costs 2006-07 – Glaucoma – category 1 (HRG code BZ19Z)	COAG model
Cost anterior chamber reformation – daycase	£556	Gamma	α = 12.03 λ = 0.015 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Cost anterior chamber reformation – inpatient	£1,776	Gamma	α = 4.41 λ = 0.0025 based on IQR	National Schedule of Reference Costs 2006-07	COAG model
Proportion of trabeculectomy daycase: inpatient	66%: 34%	none		Hospital Episode Statistics 2006/07	COAG model
Proportion of anterior chamber reformation – daycase: inpatient	46%: 54%	none		Hospital Episode Statistics 2006/07	COAG model
Discount rate (cost and QALYs)	3.5%	none		NICE reference case[107]	COAG and OHT models
Number of follow-up visits per year – COAG and treated OHT patients	4	Triangular	Min = 2 Likeliest = 4 Max = 6	Experts opinion	COAG and OHT models

Number of follow-up visits per year – OHT untreated patients	2	Triangular	Min = 1 Likeliest = 2 Max = 3	Experts opinion	OHT model
Annual probability of developing COAG – untreated	see 1.3.5	none		Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >21-25 mmHg; CCT >590µm	0.16	Beta	α = 2 β = 88	Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >25 – 32 mmHg; CCT >590µm	0.49	Beta	α = 5 β = 75	Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >21-25mmHg; CCT 555-590µm	0.73	Beta	α = 7 β = 70	Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >25-32mmHg; CCT 555-590µm	1.06	Beta	α = 10 β = 69	Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >21-25mmHg; CCT ≤555µm	1.39	Beta	α = 13 β = 65	Gordon et al (2002)[50]	OHT model
Relative Risk for progression to COAG – IOP >25-32mmHg; CCT ≤555µm	2.93	Beta	α = 28 β = 50	Gordon et al (2002)[50]	OHT model
Annual probability of progression Early to Moderate – untreated	25%	Triangular	Min = 12.5% Likeliest = 25% Max = 37.5% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007)[14]	COAG model
Annual probability of progression Early to Moderate – treated	20%	Triangular	Min = 10% Likeliest = 20% Max = 30% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007)[14]	OHT model

Annual probability of progression Moderate to Advanced – treated	7%	Triangular	Min = 3.5% Likeliest = 7% Max = 10.5% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007)[14]	COAG and OHT models
Annual probability of progression Advanced to Severe Visual Impairment – treated	6%	Triangular	Min = 3% Likeliest = 6% Max = 9% Min and max are calculated by respectively subtracting and adding half the likeliest estimate.	Burr et al (2007)[14]	COAG and OHT models
Annual probability of developing asthma in patients treated with BB	3.3%	Beta	$\alpha = 21$ $\beta = 611$	Kirwan et al (2002)[74]	COAG and OHT models
Annual probability of adding a medication after surgery	13.3%	Beta	$\alpha = 147$ $\beta = 958$	Edmunds et al (2001)[38]	COAG model
Probability of cataract extraction after trabeculectomy	2.3%	Beta	$\alpha = 29$ $\beta = 1211$	Edmunds et al (2002)[37]	COAG model
Probability of anterior chamber reformation after trabeculectomy	1.65%	none		Edmunds et al (2002){EDMUNDS 2002 and experts opinion	COAG model
Probability of natural death	function of age	none		Life Tables England and Wales	OHT and COAG models
Probability of switching treatment with BB including asthma	25%	Beta	$\alpha = 158$ $\beta = 474$	Zhou et al (2004)[166]	COAG and OHT models
Probability of switching treatment with BB excluding asthma	see 1.3.9	none		Assumption	COAG and OHT models
Probability of switching treatment with PGA	13%	Beta	$\alpha = 19$ $\beta = 130$	Zhou et al (2004)[166]	COAG and OHT models
Health utility OHT	1	none		Assumption	OHT model

Health utility Early	0.989	Triangular	Min = 0.974 Likeliest = 0.989 Max = 0.990 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the central value.	Rein et al (2007)[119]	COAG and OHT models
Health utility Moderate	0.944	Triangular	Min = 0.900 Likeliest = 0.944 Max = 0.974 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the central value.	Rein et al (2007)[119]	COAG and OHT models
Health utility Advanced	0.819	Triangular	Min = 0.712 Likeliest = 0.819 Max = 0.900 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the central value.	Rein et al (2007)[119]	COAG and OHT models
Health utility Severe Visual Impairment	0.503	Triangular	Min = 0.331 Likeliest = 0.503 Max = 0.712 where Min and Max correspond respectively to the upper and lower limits of the stage definition (in absolute terms) and the likeliest to the WHO definition of blindness	Rein et al (2007)[119]	COAG and OHT models
Health decrement with Asthma	-0.16	none		Schermet et al (2002)[130]	COAG and OHT models

RR of progression per unit of IOP reduction – OHT	0.10	1 – Log-Normal	SE = 0.037	Gordon et al (2002)[50]	OHT model
RR of progression per unit of IOP reduction – COAG	0.08	1 – Log-Normal	SE = 0.02	Leske et al (2007)[87]	COAG model

(a) When the variable is a function, its definition is reported in the referenced paragraph.

1.3.17 Results of the cost-effectiveness analysis

1.3.17.1 OHT

We found that the results of the OHT model were particularly sensitive to the age of patients at the decision point. Age is a risk factor for the development of COAG but it is also important for estimating the likelihood of visual impairment. Table 181 shows the results of the base case analysis and the one-way sensitivity analysis conducted by varying the patient's age between 40 and 80. Beyond these limits we do not have data on the probability of developing COAG.

For patients at an average age of 60, no treatment is the most cost-effective strategy if the CCT >555µm and IOP is within the 21 – 32 mmHg range. If the CCT ≤555 µm, treatment with prostaglandin analogues is the most cost-effective strategy for any IOP.

Table 14 - Results of OHT model – base case

	Mean cost (£)	**QALYs**	**Incremental cost (£) per QALY gained vs No Treatment**	**Incremental cost (£) per QALY gained vs BB**	**One-way sensitivity analysis on age**
IOP>21 – 25 mmHg, CCT>590 µm					
No Treatment	2,165	14.574	-	-	-
BB	4,748	14.586	213,504	-	Not sensitive to age
PGA	5,665	14.586	296,593	Dominated	Not sensitive to age
IOP >25 – 32 mmHg, CCT>590 µm					
No Treatment	2,872	14.471	-	-	-
BB	5,105	14.513	52,670	-	Not sensitive to age
PGA	5,934	14.522	59,805	94,182	Not sensitive to age
IOP>21 – 25 mmHg, CCT 555-590 µm					
No Treatment	3,344	14.403	-	-	-
BB	5,351	14.464	32,749	-	Not sensitive to age
PGA	6,121	14.478	36,598	52,760	Not sensitive to age

IOP >25 – 32 mmHg, CCT 555-590 µm					
No Treatment	3,940	14.316	-	-	-
BB	5,672	14.399	20,864	-	If age<60 BB is more cost-effective than no treatment.
PGA	6,368	14.421	23,124	31,650	If age<58 PGA is more cost-effective than no treatment. PGA vs BB not sensitive to age.
IOP >21 – 25 mmHg, CCT ≤555 µm					
No Treatment	4,484	14.237	-	-	-
BB	5,974	14.339	14,617	-	If age>67 no treatment is more effective than BB.
PGA	6,603	14.367	16,307	22,464	If age>65, no treatment is more cost-effective than PGA. If age<58 PGA is more cost-effective than BB..
IOP >25 – 32 mmHg, CCT ≤555 µm					
No Treatment	6,475	13.949	-	-	
BB	7,179	14.102	4,605	-	If age>80 no treatment is more effective than BB.
PGA	7,566	14.150	5,429	8,056	If age>77 BB are more cost-effective than PGA. If age >80 no treatment is more cost-effective than PGA.

The cost-effectiveness of treating OHT is strongly interconnected with the patient's risk factors for the development of COAG (age, IOP and CCT) and with the likelihood of becoming visually impaired which depends on the age at diagnosis.

In the absence of risk factors, the probability of developing COAG is so low that the little improvement in the quality of life treatment would bring does not warrant the high costs of a lifetime treatment. Not treating patients with IOP>21-25mmHg and CCT>590µm is significantly cost-effective compared to PGA as reported in Table 182, where the 95% confidence interval (CI) is above the £20,000/QALY threshold. When compared to BB, the cost-effectiveness is not significant as the lower limit crosses the £20,000/QALY threshold.

Medical treatment is cost-effective in patients with CCT≤555 µm with any IOP up to 32 mmHg and in patients with CCT 555-590 µm and IOP >25-32 mmHg. However, the 95% CI limits crossed our cost-effectiveness threshold (Table 182).

Considering only those patients for whom treatment is cost-effective, if both beta-blockers and prostaglandin analogues are available (e.g. they are not contraindicated), beta-blockers are more cost-effective if CCT 555-590 µm and IOP >25-32mmHg or if CCT<555 µm and IOP >21 – 25 mmHg while prostaglandin analogues are more cost-effective if CCT<555 µm and IOP >25 – 32mmHg. The results of the comparison between prostaglandin analogues and beta-blockers are not significant with 95% confidence (Table 182). For these groups of patients, there is an age beyond which treatment does not substantially improve the quality of life, and thus it is not cost-effective (see One-way sensitivity analysis in Table 181). For clinical simplicity, the results can be rearranged in order to round the age threshold and to limit the maximum number of age groups to two for each IOP and CCT combination. In this case after we exclude beta-blockers from the comparison, prostaglandin analogues are cost-effective up to the age of 65 in the IOP >21 – 25 mmHg and CCT<555 µm group and up to the age of 80 in the IOP >25 – 32 mmHg and CCT<555 µm group,

Table 15 - Results of PSA – OHT model

	Mean ICER (£/QALY)	95% CI – lower limit (£/QALY)	95% CI – upper limit (£/QALY)	Probability of being cost-effective at £20,000/QALY
IOP>21 – 25 mmHg, CCT>590 µm				
BB vs no treat	149,606	17,713	dominated	No Treat 97%
PGA vs No treat	649,300	64,402	dominated	BB 3%
PGA vs BB	193,576	32,110	dominated	PGA 0%
IOP >25 – 32 mmHg, CCT>590 µm				
BB vs no treat	42,773	2,801	423,141	No Treat 81%
PGA vs No treat	82,141	23,334	dominated	BB 18%
PGA vs BB	50,144	10,141	665,186	PGA 1%
IOP>21 – 25 mmHg, CCT 555-590 µm				
BB vs No Treat	28,280	942	224,519	No Treat 67%
PGA vs No Treat	50,626	15,892	11,180,850	BB 28%
PGA vs BB	32,791	6,154	271,632	PGA 5%
IOP >25 – 32 mmHg, CCT 555-590 µm				
BB vs No Treat	18,647	cost saving	138,698	No Treat 48%
PGA vs No Treat	33,040	11,036	346,902	BB 37%
PGA vs BB	21,638	3,378	152,848	PGA 15%
IOP >21 – 25 mmHg, CCT ≤555 µm				
BB vs No Treat	12,844	cost saving	89,068	No Treat 33%
PGA vs No Treat	23,184	7,466	162,175	BB 35%
PGA vs BB	15,099	1,417	93,199	PGA 32%
IOP >25 – 32 mmHg, CCT ≤555 µm				
BB vs No Treat	3,720	cost saving	38,637	No Treat 8%
PGA vs No Treat	8,277	1,460	52,186	BB 9%
PGA vs BB	4,818	cost saving	39,453	PGA 83%

1.3.17.2 COAG

Table 183 shows the results of the base case COAG model. Trabeculectomy is the most effective and most cost-effective option.

Table 16 - Results of COAG model – base case

	Mean cost (£)	QALYs	Incremental cost (£) per QALY gained vs No Treat	Incremental cost (£) per QALY gained vs BB	Incremental cost (£) per QALY gained vs PGA	Sensitivity analysis
No Treat	6,246	8.635	-	-	-	If annual probability of progression < 6% or surgical intervention costs >£1,455, trabeculectomy is not cost-effective anymore. Results not sensitive to COAG stage.
BB	6,017	8.714	cost saving	-	-	
PGA	6,113	8.745	cost saving	3,100	-	
Trab	7,247	8.849	14,679	9,113	10,906	

When the severity of the disease (COAG stage) was varied, the overall results did not change and trabeculectomy was still the most cost-effective strategy. Sensitive parameters in the model were the annual probability of progression to the following stage and the cost of trabeculectomy. When the probability of progression was lowered from 25% in the base case to 6%, trabeculectomy was not cost-effective anymore. By using the following formula we could calculate the rate in visual field deterioration corresponding to a 7% annual probability of progression:

$$\textbf{VI} \quad \text{rate} = (VF_{mod} - VF_{Early})/\text{years}$$

where

VF_{mod} = absolute value of lower bound of Moderate COAG definition (6.01dB)

VF_{Early} = absolute central value of Early COAG definition (3.00)

years = years necessary to reach Moderate COAG, calculated as

$$\textbf{VII} \quad \text{years} = 1/(\text{probability of progression})$$

The rate thus calculated was

$$\textbf{VIII} \quad \text{rate} = (6.01 - 3.00)/(1/0.06) = 0.18\text{dB/year}$$

If the visual field deteriorates at a rate lower than this value, trabeculectomy is not cost-effective.

The uncertainty over the cost-effectiveness of trabeculectomy was revealed by the results of the PSA as well (Table 184). While beta-blockers and prostaglandin analogues are significantly more cost-effective than no treatment (i.e. the upper limit is below the £20,000/QALY threshold used in our economic evaluation), the

upper limit of the ICER of trabeculectomy vs any other intervention always exceeds the £20,000/QALY threshold (Table 184).

Table 17 - Results of PSA - COAG model

	Mean ICER (£/QALY)	95% CI – lower limit (£/QALY)	95% CI – upper limit (£/QALY)	Probability of being cost-effective at £20,000/QALY
BB vs no treatment	cost saving	cost saving	9,461	
PGA vs no treatment	cost saving	cost saving	13,836	No treatment 1%
Trab vs no treatment	3,488	cost saving	57,676	BB 4%
PGA vs BB	3,079	cost saving	23,258	PGA 38%
Trab vs BB	7,483	cost saving	85,631	Trab 57%
Trab vs PGA	11,495	cost saving	122,050	

When the severity of COAG at the point of decision was increased to moderate or advanced, trabeculectomy became more cost-effective and this result less sensitive to the probability of progression. By applying a formula similar to VI, we estimated the minimum rate of visual field deterioration in order for trabeculectomy to be cost-effective in moderate COAG (0.09dB/year) and advanced COAG (0.08dB/year).

1.3.18 Discussion

The cost-effectiveness of treating OHT patients depends on their risk for development of COAG. We found that age, IOP and CCT are the clinical indicators correlated with this risk (1.3.5). According to the possible combinations of these parameters, different strategies can be cost-effective.

Beta-blockers are cost-effective for patients with IOP >25 – 32 mmHg and CCT 555 – 590 μm up to the age of 60. Prostaglandin analogues are cost-effective for patients with IOP> 21 – 25 mmHg and CCT<555 μm up to the age of 65 and for patients with IOP>25 – 32 mmHg and CCT≤555μm up to the age of 80. All other OHT patients should not receive treatment according to our analysis.

On the other hand, treating all COAG patients from an early stage is cost-effective. Results show that trabeculectomy is the most cost-effective treatment. Nevertheless being an invasive procedure it has drawbacks that we could have failed to capture in our analysis. More generally, some treatments are associated with common adverse events and complications which often require further interventions. In our model we have tried to incorporate the costs and effects of the most common and serious ones but we might have underestimated them since there is no good up to date literature on this topic.

In addition, the cost-effectiveness of trabeculectomy is conditional upon a considerable rate of progression in visual field defect. It could be worthwhile initiating medical treatment while monitoring for progression; only when a progression is detected could the patient be listed for surgery.

For patients in the later stages of COAG trabeculectomy is cost-effective even in the presence of a very low rate of progression (see 1.3.17.2) because the threat to their vision is more imminent.

We have kept some parameters conservative:

- Quality of life estimates from the selected study were generally higher than in other excluded studies.
- Increase in mortality risk due to blindness or visual impairment was not included in the model.
- The probability of developing COAG in OHT patients 70-80 years old was used also for older patients, although it was likely to be higher.
- Normal Tension Glaucoma patients were included in the IOP reduction results as well. However, including data for this population could decrease the effectiveness of treatment in reducing IOP. In fact, the effectiveness corresponds to the difference between IOP at baseline and after treatment and since their IOP at baseline is already low and drugs could be less effective in decreasing this value further.

Had we modified these assumptions, we would have favoured the most effective interventions.

However, our analysis is limited for a number of reasons:

- The OHT model is based on the findings of an RCT[50] where patients were included only if their age was between 40 and 80 years and IOP between >21and 32 mmHg. Therefore we cannot generalise our results beyond these limits.
- Some probabilities of progression were extrapolated beyond the follow-up periods cited in the literature and for advanced COAG to severe visual impairment there was no RCT data available.
- The methodology adopted by the study[119] used as the source of health utilities in the model has not been validated yet. Also, the original health utilities [12]were estimated for different ocular conditions causing a defect in visual acuity. These utilities might not be applicable to glaucoma patients since the pattern of visual loss differs from other conditions. Furthermore, generic instruments such as the EQ-5D might not completely capture the quality of life decrement caused by small changes in visual ability.

The results of our model are applicable to OHT or COAG patients who have not been treated before. Although we have included data on IOP reduction in NTG patients, we could not find any evidence on the relationship between IOP reduction and progression reduction in this population. The results of our model might not be directly applicable to these patients.

Another assumption in our model was that the severity of OHT or COAG is similar in both eyes. However, in clinical practice a patient could present with unilateral COAG or OHT. We believe that the treatment should be established according to the worse eye if treated with medical therapy. In fact, a single bottle of drops per

month is used for treating either both eyes or one eye only as the bottle should be discarded after 28 days from the opening. In addition, since it is the patient who is being treated and not the eye, the cost of follow up visits and adverse events would be the same. Conversely, a surgical approach should be adopted only for the eye that requires it.

If the results of our economic analysis were adopted in the NHS, there would be an increase in surgical treatments with more pressure on Hospital Eye Services. However, if this was accompanied by a change in the referral scheme and monitoring provision, the resources freed up by the implementation of these policies could be used for the care of those patients requiring immediate treatment to prevent further progression. In addition, OHT patients with a low risk of progression would not be treated according to our model, which saves resources in terms of drugs and visits as well as patients not receiving treatment who would be monitored less frequently. On the other hand, OHT patients at a high risk for progression would receive prostaglandin analogues which are the most effective medical treatment. As a consequence, fewer people would develop COAG with less pressure on the Hospital Eye Service and the provision of surgery.

Another consequence of our results is that more emphasis would be given to the assessment of clinical parameters such as IOP and CCT for OHT patients and visual field defect for COAG patients.

Our findings are similar to those of previous studies: Kymes et al (2006)[80] and Stewart et al (2008)[144] found that treating all OHT patients is not cost-effective, while according to Kymes et al (2006)[80] selecting those with an elevated risk of conversion to COAG is a more cost-effective strategy (see Evidence Table – Appendix D). Le Pen et al (2005)[82] explored the cost-effectiveness of prostaglandin analogues compared to beta-blockers in COAG patients through a Markov model reaching conclusions similar to our model (see Evidence Table – Appendix D).

1.3.19 Conclusions

- Treating all patients with OHT is not cost-effective.
- It is cost-effective to treat only OHT patients with IOP> 25 – 32 mmHg and CCT 555 – 590 µm with a beta-blocker until the age of 60 and OHT patients with IOP >21 and CCT ≤555µm with a prostaglandin analogue until the age of 80.

It is always cost-effective to treat COAG patients. However, trabeculectomy is cost-effective only when progression of visual field defect for Early COAG patients is >0.18 dB/per year – which is to say in the presence of any detectable progression. Trabeculectomy becomes more and more cost-effective the more advanced the stage of COAG.

1.4 NCC-AC cost analysis: Cost-effectiveness of tests

There is a wide variety of techniques and tests that are currently available for the assessment of clinical characteristics in order to diagnose and monitor OHT and COAG patients. Table 185 shows the clinical features and the relative tests used for their measurement which were included in our analysis.

Some of the tests are used for both diagnosis of OHT or COAG and monitoring. However, the importance of the result accuracy could vary between the two phases in the provision of care. CCT measurement for example is particularly important when diagnosing OHT in order to identify the relevant treatment strategy (1.3.17.1).

In our analysis, each test was compared only with the reference standard (marked in Table 185) used for the same clinical measurement.

Table 18 - Tests included in the economic analysis

Clinical Feature	Tests
IOP	Goldmann Applanation Tonometry*
	Non-contact tonometry (Pulse Air)
Optic Disc	Slit lamp biomicroscopy*
	Slit lamp biomicroscopy + stereoscopic disc photography
	Heidelberg Retina Tomography (HRT)
	Optical Coherence Tomography (OCT)
	Laser polarimetry
Visual Field	24-2 SITA Humphrey*
	Henson
	Dicon
	Octopus
	Frequency Doubling Technology
	Humphrey non-SITA
Anterior chamber angle	Gonioscopy*
	iris eclipse or shadow test
	Redmond-Smith slit lamp assessment
	Scheimpflug anterior segment photography
	Ultrasound BioMicroscopy (UBM)
	Van Herick
	A-scan
	B-scan
	Optical Coherence Tomography (OCT)

* *Reference standard*

1.4.1 General methodology

We found that the most practical approach for an economic evaluation was a cost analysis. In fact, estimating the consequences of false positives and false negatives

could be unattainable as there is uncertainty around the stage patients would be when undergoing the assessment and above all, around the time when they will be eventually correctly diagnosed. Another parameter that was not accounted for in our analysis is the time necessary to complete the tests. This exclusion is due to the following factors:

- the individual variability of the time to carry out the test,
- the consideration that while a test is being completed, the same healthcare professional could be involved in other activities,
- the variability of the opportunity cost depending on the type of healthcare professional who is performing the test,
- the GDG believed there are no substantial differences in times (with the exception of the 24-2 SITA standard Humphrey Visual Field test which we believe to be quicker than its comparators – see 1.4.5).

Consequently, we restricted our cost analysis to the calculation of capital costs, life span of the machines used, and the consumables.

We conducted a systematic search in order to identify published studies from the UK reporting cost data on the tests in Table 185 but we also relied on expert opinion and data provided by national suppliers (Haag-Streit). A study[66] was excluded because it was published in 1990 and so cost data were considered obsolete. Similarly, a decision model on screening[153] was excluded in which details of the tests which the costs refer to were not given. A HTA Kwartz et al (2005)[79] was selected as a possible source for the costs of HRT, Laser polarimetry, and Humphrey Visual Field Analyser.

Each clinical GDG member estimated the number of patients referred each year to a clinic for a confirmation of diagnosis and the number of follow-up visits. The mean of both the number of diagnostic visits and the number of follow-up visits were calculated.

Finally, we calculated the difference in cost per patient between tests measuring the same clinical feature.

Throughout the cost analysis, expert opinion was gathered from the GDG members.

1.4.2 Assumptions

The following assumptions were used in the cost analysis:

- The same test would be used for both diagnosis and monitoring
- Life span of machines is 5 years unless available data state differently
- Reference standard tests are the most accurate within the same group
- Interest rate for calculating the annual cost of machines is 3.5%
- Drugs used specifically for the test were the only consumables

1.4.3 Population

The number of patients referred every year to a clinic for confirmation/exclusion of COAG was estimated by averaging the estimates provided by the GDG (Table 186). The same method was applied to estimate the number of follow-up visits per year (Table 186). In other words, on average 3 patients per day undergo tests for the diagnosis of COAG and 33 patients per day are followed-up.

Table 19 - Population for tests

Diagnosis Population	Monitoring Population
1,000	12,000

In the cost analysis, the population for each test was the sum of diagnosis and monitoring population.

1.4.4 Resource use and costs

We could not find the capital cost of the machines used in all the tests compared. Those that were found were then used to calculate the annual cost based on the life span and the interest rate according to the formula:

$$E = K/\{[1-(1+r)^{-n}/r]+ 1\} \quad \textbf{IX}$$

where E = annual cost of the machine

K = capital outlay (cost of purchasing the machine)

r = interest rate 3.5%

n = life span

The capital cost of a Goldmann Tonometer is composed of the cost of the actual tonometer, the slit lamp on which it is mounted, and the lenses. Experts estimated the overall cost which was later confirmed by data provided by the UK supplier (personal communication). The latter also provided the average life span of the machine. The cost of a non-contact tonometer was obtained from the website of the UK distributor of Keeler Pulsair tonometer. The average life span was not available and therefore subject to assumption.

The same capital cost of the slit lamp as that which was estimated for the Goldmann Tonometer was used to calculate the cost of the slit lamp biomicroscopy test for the optic disc assessment. The cost of the HRT was found in the HTA[79] and confirmed by the UK supplier who gave us estimates of the life span as well. For the OCT we relied solely on supplier data while for the Laser Polarimetry the HTA[79] was the only available source and its life span was assumed to be 5 years. The cost of adding stereoscopic disc photography to the slit lamp examination was based on the cost of Monoscopic photography provided by the UK supplier (Haag-Streit).

No cost data were found on Visual Field tests with the exception of the Humphrey Visual Analyser. Therefore a cost analysis was not performed for this group of tests.

We obtained cost and life span data for Gonioscopy, A-scan, B-scan and OCT from the supplier. Van Herick's test is performed by means of a slit lamp, so only its cost was accounted for. Unfortunately, no cost data were obtained for the other tests.

Table 187 reports the parameters and the results of the calculation of annual costs of equipment according to the formula IX.

Table 20 - Annual cost of equipment

Machine/test	Capital outlay (K)	Life span (n)	interest rate (r)	ANNUAL COST (£)
IOP measurement				
Goldmann tonometry	10,000	15	3.5%	799
Non-contact tonometry	5,000	5	3.5%	907
Optic disc assessment				
Slit lamp biomicroscopy	10,000	30	3.5%	516
Slit lamp biomicroscopy + stereoscopic disc photography	10,000 (a)	7	3.5%	1,406
HRT	30,000	7	3.5%	4,271
OCT	45,000	7	3.5%	6,325
Laser polarimetry	30,000	5	3.5%	5,325
Anterior chamber angle assessment				
Gonioscopy	200 (b) + 10,000 (c)	3 (b) / 30 (c)	3.5%	569 (d)
A-scan	15,000	7	3.5%	2,108
B-scan	20,000	7	3.5%	2,811
OCT	28,000	7	3.5%	3,936
Van Herick	10,000 (c)	30	3.5%	516

(a) Only cost of monoscopic photography without slit lamp
(b) Gonioscope
(c) Slit lamp
(d) Total of gonioscope (£53) + slit lamp (£516)

Other resources considered in the cost analysis were drugs used in order to perform the test. One unit of Proxymetacaine and Fluorescein was used before Goldmann tonometry and Gonioscopy; whereas one unit of Tropicamide was used before Slit lamp biomicroscopy, HRT and OCT. The cost of a unit is calculated by dividing the cost of the pack by the number of units contained, as illustrated in Table 188 - Cost of drugs for tests

Table 21 - Cost of drugs for tests

Drugs	Cost Per Packa	Units	Cost Per Unit (£)
Proxymetacaine and Fluorescein	£7.95	20	0.4
Tropicamide	£5.75	20	0.3

(a) Source BNF 54

For each test, the total cost per patient was calculated as follows:

X TC = ac/p + d

where

TC = total cost per patient

ac = annual cost of equipment

p = diagnosis and monitoring population

d = cost of drug unit (if applicable)

The incremental cost per patient of a test compared to the reference standard was calculated as follows:

$$IC = TC_c - TC_{rs}$$

where

IC = incremental cost

TC_c= total cost of the comparator

TC_{rs}= total cost of the reference standard

An exception was the estimation of the incremental cost of adding stereoscopic disc photography to sit-lamp biomicroscopy which is equivalent to the cost of the photography only as the slit lamp is present in both strategies.

1.4.5 Results of the cost analysis

The incremental cost of the reference standard compared to other tests was given by the difference in the total cost per patient, as reported in Table 189.

Results for the comparison between visual field tests could not be reported since we found cost data on tests other than Humphrey.

Non-contact tonometry is cost saving compared to the more accurate Goldmann tonometry, and similarly non-gonioscopic methods are less costly than Gonioscopy (Table 189). In contrast, tests for assessing optic disc are associated with increased costs (Table 189) without adding valuable or more accurate information on the clinical picture of the patient (expert opinion) when compared to the Slit lamp

biomicroscopic examination. On the other hand, adding stereoscopic disc photography to the slit lamp examination generates an additional cost per patient of 0.11 but could also provide useful information.

Table 22 - Results of cost analysis of tests

Test	Cost per patient (£)	Cost of test – cost reference standard (£)
IOP measurement		
Goldmann tonometry*	0.46	-
Non-contact tonometry	0.07	- 0.39 (cost saving)
Optic disc assessment		
Slit lamp biomicroscopy*	0.33	
Slit lamp biomicroscopy + stereoscopic disc photography	0.44	0.11
HRT	0.62	0.29
OCT	0.77	0.44
Laser polarimetry	0.41	0.08
Anterior chamber angle assessment		
Gonioscopy*	0.44	-
A-scan	0.16	-0.28 (cost saving)
B-scan	0.22	-0.22 (cost saving)
OCT	0.30	-0.14 (cost saving)
Van Herick	0.04	-0.40 (cost saving)

* *Reference standard*

1.4.6 Discussion

The first test that a patient receives at a diagnosis or monitoring visit is tonometry, which is a measurement of IOP. The Goldmann contact-tonometer is considered the reference standard. Whereas other non-contact tonometers are less costly (1.4.5) they are also less accurate. The consequences of obtaining a correct IOP measurement are closely connected to the identification of the most cost-effective treatment strategy (see 1.3). Therefore, despite its higher direct costs, Goldmann tonometry could be cost-effective compared to non-contact tonometry.

Anterior chamber angle assessment is fundamental at diagnosis in order to differentiate between open angle and angle closure glaucoma. It becomes less important at follow-up visits. Our analysis shows that gonioscopy is more costly than non-gonioscopic methods including Van Herick's test when omitting the cost of false referral and incorrect therapy initiation. Because of its elevated accuracy, it was the GDG's opinion that the reference standard cannot be substituted at diagnosis. However, for monitoring purposes van Herick's test could be sufficient. Gonioscopy is not extensively used in current practice and many optometrist practices in the community are not equipped to perform this test. Community Optometrists could

choose between purchasing a gonioscopy contact lens themselves and participating in a Hospital Eye Service (HES) scheme where this equipment would be provided.

Among the methods which are practical for routine use in the NHS, stereoscopic slit lamp biomicroscopy is considered the most reliable investigation to identify optic nerve damage from its appearance. In our cost analysis stereoscopic slit lamp examination turned out to be less costly than HRT, OCT and Laser Polarimetry. When this result is combined with its reputed greater accuracy, stereoscopic slit lamp biomicroscopy dominates the other tests. A further comparison in the analysis was made between the reference standard alone and the reference standard plus stereoscopic disc photography. This technology is not available in the current practice and to date it is only used in clinical trial settings. The additional costs that were found in the cost analysis (1.4.5) could be even higher since they correspond to the costs of monoscopic photography. Identifying optic disc damage is important for the correct diagnosis of COAG; if the damage is not identified the patient risks being discharged at serious risk of delayed diagnosis and treatment.

Our cost analysis has several limitations:

- We were not able to evaluate any estimate of effectiveness associated with each strategy; therefore a cost-effectiveness analysis could not be conducted.
- The cost of misdiagnosing OHT or COAG could be significant but was omitted because it would be very hard to estimate with reasonable precision. (The costs associated with correct diagnoses were also omitted).
- The harms caused by some tests (e.g. infections from Goldmann tonometer) and their costs were not included in the analysis.
- The final consideration on the accuracy of the tests (i.e. the reference standards are the most accurate) was largely based on expert opinion rather than on solid clinical evidence.

Unfortunately we did not find any study that carried out a similar economic analysis, thus we could not compare our findings with previous data.

1.4.7 Conclusions

- Goldmann tonometry and gonioscopy are considered the most accurate for the assessment of IOP and anterior chamber angle respectively. However they also generate more costs compared to non-contact tonometry and to non-gonioscopic methods.
- Stereoscopic slit lamp biomicroscopic assessment is considered the most accurate test for identifying optic nerve damage and it is also associated with less costs compared to HRT, OCT and Laser Polarimetry.
- These results should be treated with caution since the analysis has several limitations.

Appendix G

Recommendations for research

1.1 Recommendations for research on monitoring patients with OHT, COAG and suspected COAG

PICO question	Question: What is the clinical and cost effectiveness of different monitoring intervals for detection of disease progression in COAG patients at risk of progression?
Importance to patients or the population	Detection of progression of visual field damage in COAG is essential if treatments to prevent progression are to be instituted in time to avoid eventual deterioration to permanent severe visual impairment.
Relevance to NICE	The answer to this question is key to guidance on chronic disease monitoring intervals in this guideline. Once diagnosed COAG patients face lifelong monitoring and treatment. Monitoring intervals tailored to the risk of progression for varying risk strata would allow more efficient use of available resources. Risk guided intervals would allow those at high risk of progression to receive more intensive monitoring and relieve the burden of unnecessary monitoring visits on those with slowly progressive disease. Resources would be more appropriately focused on those at greatest risk and with more effective early detection of progression, damage to vision over time may be minimised. With this information available NICE would be in a position to recommend risk guided monitoring intervals resulting in both better use of resources and better outcomes.
Relevance to the NHS	The NHS would be in a better position to focus resources on those in most need. Early detection of progression followed by effective intervention would ultimately result in better visual outcomes and less costs associated with supporting visually impaired people (glaucoma currently accounts for ~10% of blind / partial sight registrations in England).
National priorities	Improving chronic disease management is currently an NHS priority[33]. This DH policy document specifically identifies "Stratifying patients by risk" and "Aiming to minimise unnecessary visits" as 2 of its key priorities, each of which is relevant to this research question.

Current evidence base	No trial evidence was identified
Study design	*Design*: A randomised comparative trial of 3 perceived risk strata (rapid, medium, slow) for progression to be randomised to 2, 3 and 2 alternative monitoring intervals respectively. *Outcome*: Progression events detected.
Feasibility	The research would be ethically and technically feasible. The research costs would need to be considered in the context that participants would still need monitoring if outside a trial.
Other comments	The National Institute for Health Research (NIHR) might be a suitable funding source.
Importance	High. The research is essential to inform future updates of key recommendations in the guideline.

1.2 Recommendations for research on treatment for patients with COAG

1.2.1 Update of National survey of trabeculectomy

PICO question	What are the current NHS national benchmarks for surgical success and complications in patients with COAG undergoing trabeculectomy drainage surgery with and without pharmacological augmentation?
Importance to patients or the population	This would inform patients of what to expect from their surgery in terms of the chances of success and complications. It would provide more accurate and up to date evidence for surgical treatment in glaucoma.
Relevance to NICE	Changes in surgical technique, and therefore success and complication rates, could alter the economic model for glaucoma treatment resulting in potential changes in the NICE recommendations
Relevance to the NHS	Up to date information on surgical success and complication rates will provide benchmarks for clinical audit and assist in planning service provision.
National priorities	Not a national priority in term of NSF or white paper
Current evidence base	Current evidence base is the National Audit of Trabeculectomy. This is now 10 years old and techniques have changed. Some surgeons are advocating the use of other surgical techniques such as deep sclerectomy and drainage tube implants. The audit would set a standard against which newer techniques could be evaluated.
Study design	The study design should be the same as the Audit of 10 years ago so we can compare the outcomes now in the light of changes in technique and the recommendations made by that audit.
Feasibility	Technically, ethically and financially feasible
Other comments	The research could be facilitated by the Royal College of Ophthalmologists. The National Institute for Health Research (NIHR) might be a suitable funding source. The Connecting for Health Information Centre may be a further source of support.
Importance	High. The research is essential to inform future updates of key recommendations in the guideline.

1.2.2 Laser treatment

PICO question	What is the effectiveness and cost-effectiveness of initial argon, diode or selective laser trabeculoplasty treatment compared to PGA alone or laser + PGA in combination in COAG patients?
Importance to patients or the population	The comparative effectiveness and cost effectiveness of laser treatment compared to modern ocular hypotensive agents particularly PGAs are unknown but may offer a period of pressure control without the need for topical medications in some patients. In others, it may offer additional benefit to topical medications and in both cases there may be cost efficiencies and improved prevention of progression of the disease
Relevance to NICE	Because of the lack of evidence, the role of laser trabeculoplasty in COAG management cannot be clearly defined.
Relevance to the NHS	Knowledge of comparative effectiveness to modern medications may offer a significant gain in cost benefit and might lead to a major change in guidance for a significant proportion of newly diagnosed COAG patients
National priorities	Treatment of long term conditions
Current evidence base	A completed Cochrane systematic review clearly points to the need for up to date evidence as indicated above. Existing trials of laser trabeculoplasty compared to medical treatment refer to outdated pharmacological agents.
Study design	RCTs in primary research
Feasibility	The research would be ethically and technically feasible.
Other comments	MRC or NIHR would be suitable sources of funding as opposed to manufacturers of medicines or lasers. To enable double masking or at least single masking, some form of sham laser treatment will be needed.
Importance	High. The research is essential to inform future updates of key recommendations in the guideline.

1.3 Recommendations for research on service provision

PICO question	In patients identified on primary examination as exhibiting possible COAG, OHT or glaucoma suspect status, what is the comparative effectiveness of diagnosis by different healthcare professions?
Importance to patients or the population	High. Further involvement of non-medical healthcare professions in care of patients within the scope of this guideline has potential to increase available staff resource with the potential to improve access to care, both in terms of number of available clinicians and locations.
Relevance to NICE	An answer to this question might potentially alter the service deliver recommendations of the current guideline. This is important in the context of access to care.
Relevance to the NHS	High. The initial guideline recommends that patients within its scope receive care following diagnosis as well as the setting of a management plan, supervised by an NHS consultant ophthalmologist. This research recommendation aims to determine whether alternative options exist. Dependent on findings, it is possible that provision of care by non-medical professionals may impact the NHS in terms of cost and quantity of care available, and may require strategic service planning to determine future staffing requirements.
National priorities	Improving chronic disease management is currently an NHS priority[33]. This DH policy document specifically identifies "Stratifying patients by risk" and "Aiming to minimise unnecessary visits" as 2 of its key priorities, each of which is relevant to this research question.
Current evidence base	The current available evidence base in the area is weak. One RCT exists, but is of limited generalisability due to its design.
Study design	A number of randomized controlled trials will be required.
Feasibility	The research would be ethically and technically feasible. However, due to the nature of the question, it is likely that projects in question will be large scale, require large sample sizes over extended time periods (years) and as such the research will be costly.
Other comments	No large scale service provision primary research on this subject area has been executed in over 10 years although the DH did pilot alternative glaucoma care pathways, demonstrating central government interest in this subject area.
importance	High: the research is essential to inform future updates of key recommendations in the guideline.

1.4 Recommendations for research on information for patients

PICO question	What is the clinical and cost effectiveness of providing glaucoma patients with a 'glaucoma card' or individual record of care compared to standard treatment?
Importance to patients or the population	Patient involvement in and understanding of management of glaucoma could reduce stress and uncertainty for patients and potentially improve compliance with medical treatment requirements, with resultant improved outcome i.e. prolonged sighted lifetime.
Relevance to NICE	This could provide evidence of better care in terms of outcome and patient experience. As such future NICE guidance would be in a position to recommend this more patient focused approach to care.
Relevance to the NHS	This could enable a significant increase in cost effectiveness by improving glaucoma management e.g. maximising the effectiveness of topical medical treatment across more patients.
National priorities	Improving chronic disease management is currently an NHS priority[33]. This DH policy document specifically identifies "Stratifying patients by risk" and "Aiming to minimise unnecessary visits" as 2 of its key priorities, each of which is relevant to this research question.
Current evidence base	No RCTs or systematic reviews were identified in our literature review addressing this question.
Study design	Randomised controlled trial design with a qualitative component. The latter would be needed to develop both an appropriate intervention and patient focused outcome measure to assess patient experience. A standard visual function (field of vision) test would be appropriate for evaluation of visual outcome.
Feasibility	Ethically and technically feasible. The proposed studies would require significant simple size and duration to determine visual outcome with associated cost implications.
Other comments	Time scale to assess useful outcomes would be long, probably 5 years or more.
Importance	Medium. The research is relevant to the recommendations in the guideline but the research recommendations are not key to future updates. Anything that improves concordance with medications could help prolong a person's sight.